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THE MECHANISM OF THE BENZIDINE AND RELATED REARRANGEMENTS

A THESIS

Presented to

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Michael Fred Dunn

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THE MECHANISM OF THE BENZIDINE AND RELATED REARRANGEMENTS

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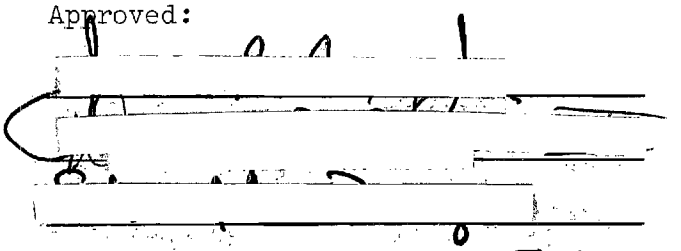

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SUMMARY

The research efforts described in this thesis were initiated with the intention of gaining further insight into the nature of the transition state and/or intermediates in the vicinity of the rate-limiting step of the benzidine rearrangement which would provide direct experimental evidence that would differentiate between Ingold's polar transition-state theory and Dewar's π-complex theory.

The approach to this problem has been to investigate a series of analogs of hydrazobenzene, through their synthesis and through a detailed investigation of their suspected rearrangements. This approach has resulted in the discovery of five new rearrangements which appear to be mechanistically related to each other and to the benzidine rearrangement.

Thus an investigation of the reaction of N-acetylphenylhydroxylamine with diphenyl iodonium hydroxide to yield 4'-hydroxy-4-acetamidobiphenyl shows, by means of oxygen-18 labeling experiments, that the reaction occurs via the intermediacy of O,N-diphenyl-N-acetylphenylhydroxylamine which spontaneously rearranges to the afore-mentioned products under aqueous, basic conditions.

It is concluded that the facile rearrangement of O,N-diphenyl-N-acetylhydroxylamine is a result of an inductive electron impoverishment of the nitrogen-oxygen bond. This inductive effect is attributed to the cumulative effects of the N-acetyl substituent and the greater electronegativity of oxygen as compared to nitrogen. In accord with this

conclusion, it was found that the rate of rearrangement of N-acetylhydrazobenzene to N-acetylbenzidine in concentrated perchloric acid-sodium perchlorate solutions has a first-order dependency on the Hammett acidity. Deuterium labeling experiments were carried out on this rearrangement which characterize it as an intramolecular rearrangement and a true manifestation of the benzidine rearrangement.

Investigation of the nature of the acetanilide-like portion of these systems resulted in the finding that N-acetyl-N-phenylhydroxylamine reacts with one equivalent of p-toluenesulfonyl chloride at -5 to 0° in a basic aqueous-acetone solution to afford the tosylates of o- and p-hydroxyacetanilides in yields of 63 and 10 per cent respectively. The remainder of the p-toluenesulfonyl chloride was accounted for as sodium p-toluenesulfonate. A similar reaction was observed with methanesulfonyl chloride, trifluoroacetic anhydride and dichloroacetyl chloride. The reaction of N-acetyl-N-phenylhydroxylamine with dichloroacetyl chloride was found initially to form O-dichloroacetyl-N-acetyl-N-phenylhydroxylamine which could be isolated unrearranged as a viscous liquid. Kinetic studies, via n.m.r., of the rearrangement of this material to the dichloroacetates of o- and p-hydroxyacetanilides in yields of 75 and 25 per cent respectively in dichloroacetic acid and methoxyacetic acid indicated that the rearrangement is intramolecular. Oxygen-18 labeling studies on the course of this rearrangement in dichloroacetic acid substantiated the intramolecularity of the rearrangement, and furthermore, demonstrated that the carbonyl oxygen and the hydroxylamine oxygen become chemically equivalent during the course of the rearrangement. Significantly, it was found that O,N-diacetyl-N-phenylhydroxylamine and

O-p-nitrobenzoyl-N-acetyl-N-phenylhydroxylamine did not undergo rearrangement, and thus rearrangement is dependent on the electron-withdrawing strength of the sulfonyl or acyl substituent.

It is concluded that these rearrangements are good mechanistic analogies of the benzidine rearrangement, and that these rearrangements provide good evidence for a heterolytic bond cleavage in the benzidine rearrangement and that they lend considerable support to Ingold's polar transition state theory. The rearrangement of the O-solfonyl and O-acyl derivatives provide direct evidence against the Dewar π-complex theory.

A review of the chemical literature pertaining to the mechanism of the benzidine rearrangement, the nitramine rearrangement and related rearrangements is presented, and a generalization of Ingold's polar transition state theory is proposed as a common mechanistic rationale for the benzidine rearrangement, the nitramine rearrangement, the quinamine rearrangement and the new rearrangements presented in this thesis.

CHAPTER I

INTRODUCTION

The study of molecular rearrangements has been, and continues to be, an area of exceptional interest to the theoretical organic chemist. An enormous amount of effort in recent years has been expended toward the elucidation of the intimate details of many of the known intramolecular rearrangements. However, in spite of the intense research activity in this area, the mechanistic interpretation of the majority of these rearrangements is rife with controversy.

The elusive nature of intramolecular rearrangements stems from the inability of current mechanistic theories, which are well suited to the description of intermolecular reactions (i.e. nucleophilic and electrophilic substitution and radical reactions), to describe many intramolecular rearrangements (i.e. Wagner-Meerwein rearrangements, Cope rearrangements, Claisen rearrangements, the nitramine rearrangement, the Favorskii rearrangement and the benzidine rearrangement to mention only a few.)

In each instance, the controversy arises about the nature of the transition state and/or intermediate which lies along the reaction coordinate between the scission of the old bond in the unrearranged material and the formation of the new bond in the rearranged product.

The solution to this problem depends on the design of experiments which allows a more subtle probing into the nature of the transient

forces which are responsible for holding the rearranging fragments together during migration. The insight gained from such experiments will provide the information necessary for the refinement of current mechanistic theories and the development of more satisfying descriptions of intramolecular processes.

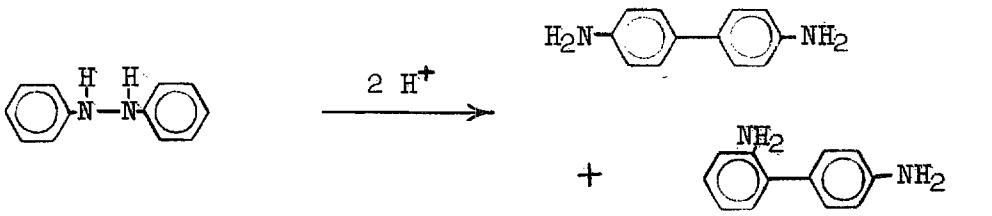
The primary problem considered in this thesis is the mechanism of the benzidine rearrangement. The research work described in this thesis was incepted with the intention of providing new experimental evidence relevant to the nature of the bonding in the rate-limiting transition state and/or intermediate of this reaction by investigating analogs of hydrazobenzene. It was hoped that this approach would make possible a better understanding of the poorly understood transition state bonding and thus strengthen our theoretical knowledge of intramolecular reactions.

CHAPTER II

HISTORICAL BACKGROUND

The Mechanism of the Benzidine Rearrangement

The acid catalyzed conversion of hydrazobenzene to benzidine (70 per cent) and diphenyline (30 per cent), discovered by Hofmann[1] in 1863 (Eq. 1), has been the subject of extensive investigation in recent years and the scope and mechanism of this intriguing transformation has been the subject of several reviews.[2,3]



(Eq. 1)

Therefore it will be sufficient here to restrict discussion of the benzidine rearrangement to a discussion of only that portion of the abundant literature which directly concerns the salient features of the mechanism of the rearrangement.

The intramolecularity of the benzidine rearrangement was implied by the early work of Jacobson,[4] who noted that dissymmetric

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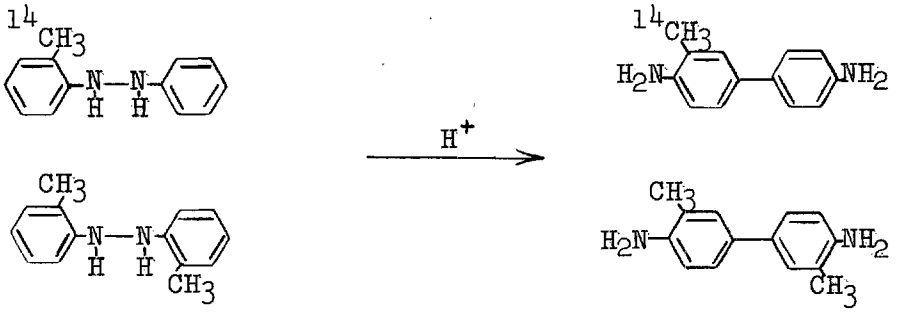
(1) A. W. Hofmann, Proc. Roy. Soc., (London), 12, 576 (1863).
(2) M. J. S. Dewar in "Molecular Rearrangements", ed. P. deMayo, V. 1, Interscience Publishers, 1963, pp. 295.
(3) D. V. Banthorpe, E. D. Hughes and C. K. Ingold, J. Chem. Soc., 1964, 2864.
(4) P. Jacobson, Ann., 428, 76 (1922).

arylhydrazines gave upon rearrangement only dissymmetric products. This observation excludes a homolytic but not a heterolytic intermolecular dissociation mechanism. Ingold and Kidd[5] established semi-quantitatively the intramolecularity of the transformation through the rearrangement of a mixture of two dissymmetric arylhydrazines to yield only products derived from intramolecular processes. Finally, the intramolecular character of the benzidine rearrangement was unambiguously established by the classical studies of Smith, Schwartz and Wheland[6] in 1952. They rearranged a mixture of 2,2'-dimethylhydrazobenzene and 2-methyl-^{14}C-hydrazobenzene and demonstrated that the resulting 3,3'-dimethylhydrazobenzene was uncontaminated (less that 0.03 per cent) by radioactive carbon from intermolecular processes. Proof of the purely intramolecular nature of the benzidine rearrangement has been extended to the hydrazo-



(Eq. 2)

naphthalene series by the recent work of Banthorpe.[7]

The early kinetic work of van Loon[8] in 1904 first demonstrated that the rearrangement is third order overall, second order with respect to hydrogen ions and first order with respect to substrate. For reasons

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(5) C. K. Ingold and H. V. Kidd, J. Chem. Soc., 1933, 984.
(6) D. H. Smith, J. R. Schwartz, and G. W. Wheland, J. Am. Chem. Soc., 74, 2282 (1952).
(7) D. V. Banthorpe, J. Chem. Soc., 1962, 2413.
(8) J. P. van Loon, Rec. trav. chim., 23, 62 (1904).

unknown, however, this work, for the most part, has escaped notice and thus in 1950 Hammond and Shine[9] "rediscovered" the second-order dependency on hydrogen ions after earlier workers[10,11] failed to test the hydrogen ion dependency in their kinetic studies on the rearrangement. It was found also by thses workers[9] that the rate of the rearrangement is subject to a large positive salt effect. Hammond and Cohen's[12] subsequent kinetic studies were offered as evidence for general acid catalysis, but the non-linearity of their plots suggest that they actually were observing a dependency on the Hammett acidity of their solutions, since the specific third-order rate constants were found to increase markedly as the acid concentration increased. That this is indeed the case, has been demonstrated by the more recent work of Ingold, et al.[13] This work definitely supports specific acid catalysis for both of the kinetically required protons. Their evidence for the pre-equilibrium transfer of both protons resides in the observation that the rearrangement of hydrazobenzene is subject to one of the largest solvent deuterium isotope effects yet observed (k_D/k_H = 4.7). If the rearrangement were subject to general acid catalysis, then a retardation of the rate of reaction would be expected. Furthermore, these workers[13] found that the examples of the benzidine rearrangement which they studied (including hydrazobenzene) were a function of the Hammett acidity of their

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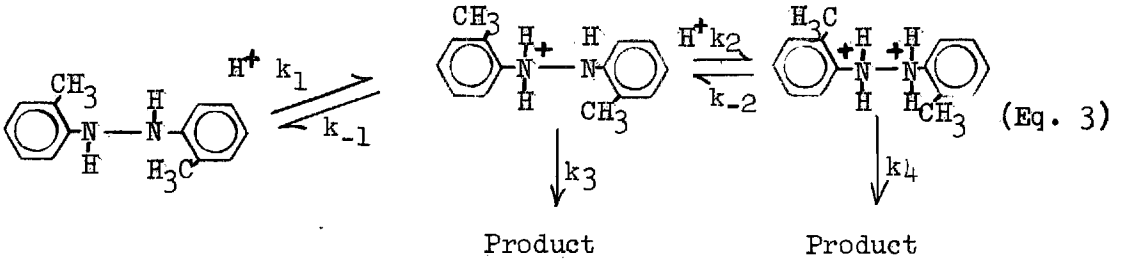
(9) G. S. Hammond and H. J. Shine, J. Am. Chem. Soc., 72, 220(1950).
(10) M. J. S. Dewar, J. Chem. Soc., 1946, 777.
(11) E. Biilmann and J. H. Blom, J. Chem. Soc., 125, 1719 (1924).
(12) G. S. Hammond and M. D. Cohen, J. Am. Chem. Soc., 75, 880 (1953).
(13) D. V. Banthorpe, E. D. Hughes and C. K. Ingold, J. Chem. Soc., 1962, 2386.

solutions rather than the hydrogen ion concentration, at hydrogen ion concentrations where the deviations between the two acidity scales become significant. Although this observation by itself does not categorically rule out general acid catalysis, it does augment the conclusions drawn from the large solvent deuterium isotope effect, and the two observations taken together strongly support a specific hydrogen ion catalysis mechanism.

The discovery made by Carlin and Odioso[14] in 1954, that o-hydrazotoluene exhibits an apparent order in hydrogen ion concentration of 1.6 in alcoholic hydrogen chloride, was rationalized by Blackadder and Hinshelwood[15] in 1957 in terms of the following mechanism:



(Eq. 3)

which leads to the rate expression:

$$v = k[\text{Hydrazo}][H^+] + k'[\text{Hydrazo}][H^+]^2 \qquad \text{(Eq. 4)}$$

Dewar,[16] in 1959, suggested an alternative kinetic scheme in which the rate of formation of a mono-protonated Π-complexed

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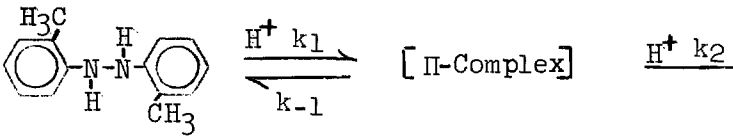
(14) R. B. Carlin and R. C. Odioso, J. Am. Chem. Soc., 76, 100 (1954).

(15) D. A. Blackadder and C. Hinshelwood, J. Chem. Soc., 1957 2898.

(16) M. J. S. Dewar, "Theoretical Organic Chemistry, Kekule Symposium", Butterworths Scientific Publications, London, 1959, p. 195.

intermediate and the rate of the acid-catalyzed conversion of this complex to products are comparable and rate-determining, thus causing the apparent hydrogen ion dependency to be a function of the relative velocities of both steps, the second velocity being, in turn, a function of the acid concentration. Dewar's mechanism is shown in Eq. 5:



(Eq. 5)

and leads to the rate expression:

$$v = \frac{k_1 k_2 [\text{Hydrazo}][H^+]^2}{k_{-1} + k_2[H^+]} \qquad \text{(Eq. 6)}$$

This scheme was subsequently proven incorrect by the kinetic studies of Ingold's group[17-21] and also by the work of White and Preisman.[22] Ingold's group discovered, while investigating the rearrangements of a series of hydrazonaphthalenes, that the rearrangements of 1,1'-hydrazonaphthalene and 1,2'-hydrazonaphthalene are second-order reactions, first order with respect to substrate and first order with respect to hydrogen ion concentration (or more exactly first order with respect to the Hammett acidity h_o).

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(17) D. V. Banthorpe and E. D. Hughes, J. Chem. Soc., 1962,2402.
(18) D. V. Banthorpe, ibid., 1962, 2407.
(19) D. V. Banthorpe, E. D. Hughes and C. K. Ingold, ibid., 1962, 2418.
(20) D. V. Banthorpe, ibid., 1962, 2429.
(21) D. V. Banthorpe, C. K. Ingold, J. Roy and S. M. Somerville, ibid., 1962, 2436.
(22) W. N. White and R. Preisman, Chem. Ind. (London),1961, 1752.

They[13] also found that the rearrangements of 2,2'-hydrazonaphthalene, phenyl-α-naphthylhydrazine and phenyl-β-naphthylhydrazine exhibit apparent orders in acid which vary between one and two with increasing hydrogen ion concentration. Reinvestigation of the work done by Carlin and Odioso demonstrate that the rate of rearrangement of o-hydrazotoluene also has a hydrogen ion dependency which varies between one and two with increasing acid concentration. These observations, as the authors have pointed out, are in full accord with the Blackadder-Hinschelwood scheme. The scheme proposed by Dewar predicts just the opposite--a decrease in the apparent kinetic dependence with increasing hydrogen ion concentration. The product ratios which were obtained for these examples of variable hydrogen ion dependency were, not unexpectedly, also a function of the hydrogen ion concentration.

In addition, Ingold's group[20,21] found that the solvent deuterium isotope effect also increases with the hydrogen ion concentration. The magnitudes of the effect were found to average to a value of $k_D/k_H = 2.3$ per proton, supplying additional evidence for a specific hydrogen ion catalysis mechanism.

Banthorpe and Hughes[23] found that the rate of reaction and the product distribution for the rearrangement of hydrazobenzene are unaffected by either 4,4'-dideuteration or 2,3,5,6,2',3',5',6'-octadeuteration, in good agreement with the earlier observations of Hammond and

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(23) D. V. Banthorpe and E. D. Hughes, J. Chem. Soc., 1962, 3308.

Grundemeier.[24] However, there was observed an effect on the ratios of products obtained from the rearrangement of 1,1'-hydrazonaphthalene on 2,2'-dideuteration, although no effect upon the rate of the rearrangement could be measured. This fact is a clear indication that, at least in this example of the benzidine rearrangement, the product-controlling step of the rearrangement occurs after the rate-determining step. Hammond and Clovis[25] found, in an interesting study on the rearrangement of m-hydrazoaniline containing nitrogen-15 labeled hydrazo nitrogens, that the nitrogen-15 distribution in the product was intermediate between that expected for the exclusive occurrence of either para or ortho couplings, and thus both must be taking place. The ratio of ortho to para coupling was found to be a function of the acid strength with the per cent ortho coupling increasing as the acid concentration increased. This information is in accord with the above observation that the rate-determining step and the product-determining step can be different, since Hammond and Clovis found that the rate dependency on hydrogen ions remained the same over the range of acidities under which the nitrogen-15 studies were carried out. Unfortunately, the strong basicity of m-hydrazoaniline complicates the form of its kinetic dependency in hydrogen ions, and the rearrangement follows an apparent inverse dependence. It is probable that there occurs only a single protonation prior to the rate-determining step in this example, with

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(24) G. S. Hammond and W. Grundemeier, J. Am. Chem. Soc., 77, 2444 (1955).

(25) G. S. Hammond and J. S. Clovis, Tetrahedron Letters, 945 (1962).

the variation in the ratio of ortho to para coupling in the product-determining steps arising from a second, kinetically unimportant protonation.

Dewar[16] has offered simple rules for the prediction of substituent effects upon the type of products (e.g. a benzidine, a 2,4-diphenyline or an ortho-semidine) to be expected from the rearrangement of substituted hydrazobenzenes. Ingold, et al.,[3] have recently reconsidered this aspect of the benzidine rearrangement and have published a more detailed set of rules which appear to accommodate better the wealth of data present in the literature. Ingold's rules may be summarized as follows:

1.) A single 4-substituent which is a strong electron donating group (either through resonance interaction or inductive interaction) will result in the preponderance of the ortho-semidine product derived from 2,N'-linkage. Substituents in this classification are methyl, methoxy, and ethoxy.

2.) A single 4-substituent which is either weakly electron donating or electron withdrawing will result in the preponderance of 2,4'-diphenyline formation. Substituents in this class are acetoxy, dimethylammonium and hydrogen.

3.) When two different substituents are present in the 4- and 4'-positions, ortho-semidines are produced and the ortho-semidine which is formed is controlled by the more electron donating substituent, with 2,N'-linkage taking place in its own ring. Thus the following substituents take precedence in the order shown: $EtO- > CH_3- > AcO-$, $I-$, HMe_2N^+-.

4.) 3,3'-Disubstitution and 2,2'-disubstitution as well as 3-monosubstitution and 2-monosubstitution lead to the exclusive formation of the corresponding 4,4'-linked benzidines.

Several uncatalyzed benzidine-like rearrangements have been observed (for example, the thermal rearrangement of 1,1'-hydrazonaphthalene to the 2,2'-linked benzidine)[26] and have been shown to be intramolecular. The rate of the rearrangement of 1,1'-hydrazonaphthylene[26] has been found to be very sensitive to solvent polarity, suggesting that there is considerable polar character to the transition state of the rearrangement. Banthorpe and Hughes[26] have investigated the substrate deuterium isotope affect on both the rate and the product ratios on this rearrangement, and they have found that 2,2'-dideuteration (but not 4,4'-dideuteration) reduces the rate (k_H/k_D = 1.18 in ethanol at 70°) and also reduces the formation of 2,2'-linked products, in marked contrast to the acid-catalyzed rearrangement.

At this point, a fairly detailed, although incomplete, composite picture of the benzidine rearrangement can be constructed from the preceeding accumulation of experimental observations. This picture is outlined on the following page (Eq. 7). 2,2'-Dimethylhydrazobenzene is used to illustrate the kinetic forms of the three concurrent reactions which characterize the rearrangement, although 2,2'-dimethylhydrazobenzene has been shown to obey only the two acid catalyzed kinetic forms.

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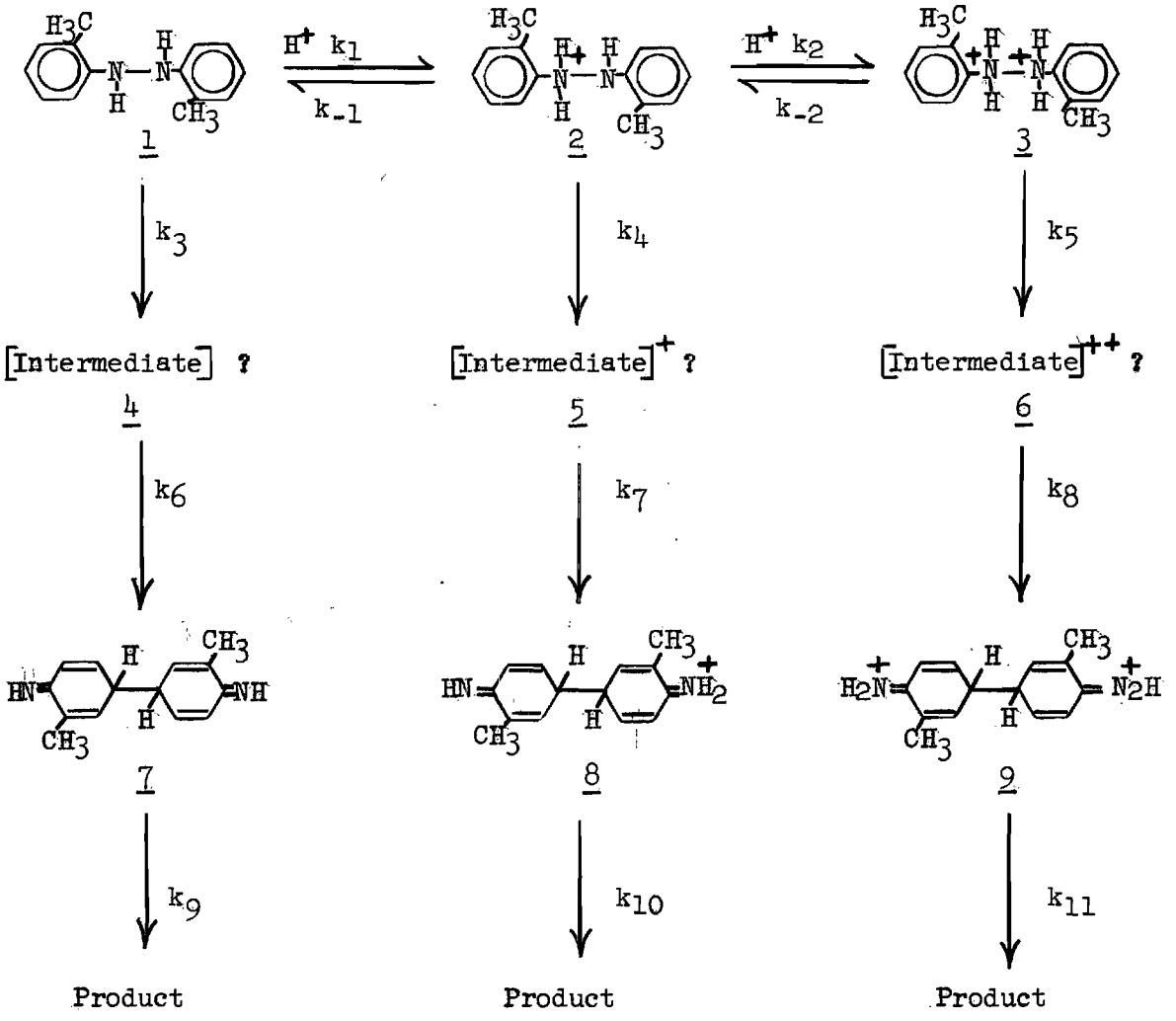
(26) D. V. Banthorpe and E. D. Hughes, J. Chem. Soc., 1964, 2849.



The reversibility of steps k_1 and k_2 is intuitively reasonable, since proton transfers of this type usually have rate constants of the order of 10^5 - 10^8 liters mole^{-1} sec.$^{-1}$ in protic media[27] (although the rate of exchange of the trimethylammonium ion[27] proton in aqueous solution is given as 6×10^{-2} liters mole^{-1} sec.$^{-1}$).

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(27) J. Hine, "Physical Organic Chemistry", second ed., McGraw-Hill Inc., Maple Press Co., York Pa., 1962, pp. 113.

Cleavage of the nitrogen-nitrogen bond in steps k_4 and k_5 for the one and two proton pathways respectively is likely the rate-limiting step in each instance, however, this has yet to be demonstrated explicitly. The driving force for the rearrangement clearly arises from the bond stabilization energy advantage gained on proceeding from reactants to products as a result of the low bond energy (approximately 60 Kcal/mole) for the nitrogen-nitrogen bond. Nitrogen-nitrogen bond cleavage in the two proton pathway is envisaged to result from the coulombic repulsions exerted by the adjacent positive charges in intermediate 3, thus accounting for the observed acid catalysis. The stimulus for nitrogen-nitrogen bond cleavage in the thermal and one proton pathways is less obvious and discussion of this point is deferred until discussion of the proposed rearrangement mechanisms is made.

That the re-aromatization proton transfer steps k_{10} and k_{11} are fast in protic solvents relative to the corresponding rate-limiting steps k_4 and k_5 could not have been predicted, but the lack of a substrate deuterium isotope effect on the rate of rearrangement and also on the product ratios in those examples which have been examined in detail clearly supports a rapid proton loss from the σ-complexes 8 and 9. The small substrate deuterium isotope effect on the rate of the thermal rearrangement of 1,1'-hydrazonaphthalene suggests that the rate-limiting transition state of the rearrangement may involve bonding interactions between the 2- and 2'- positions as well as nitrogen-nitrogen bond scission. The rate of the re-aromatization proton transfer step (k_9) of the neutral σ-complex 7 is clearly expected to be much slower than the corresponding steps k_{10} and k_{11} in the one and

two proton pathways.

The nature of the rate-limiting steps k_4 and k_5 and the possible formation of intermediates before σ-complex formation have been the subject of much speculation over the years, since the unusual stereochemistry of the benzidine rearrangement defies simple application of the London[28] treatment, due to the excessive bonding distances such a picture invokes. The London treatment describes a transition state as a resonance hybrid of those bonds of the initial and final states which become exchanged in the reaction.

In 1945, Dewar[29] first proposed his Π-complex mechanism as a common rationale for a variety of rearrangements which formally involve the migration of a moiety attached to the nitrogen of an aniline derivative into the aromatic ring. The Π-complex mechanism as first proposed for the benzidine rearrangement assumed a first-order dependency in hydrogen ion. Thus Dewar was forced to modify his picture from that of a monoprotonated Π-complexed species which underwent subsequent product-forming steps, to a monoprotonated Π-complex which underwent an acid-catalyzed transformation to products as the rate-limiting step[16] and finally to a diprotonated Π-complex which undergoes subsequent product-forming steps.[30] The diprotonation requirement considerably weakens Dewar's Π-complex argument, since the simple picture of electron-rich

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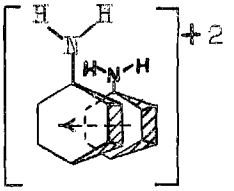
(28) F. London, Z. Elektrochem., 35, 552 (1929).
(29) M. J. S. Dewar, Nature, 176, 784 (1945).
(30) M. J. S. Dewar and A. P. Marchand, "Physical Organic Chemistry: Π-Complexes as Intermediates in Organic Reactions," Unpublished manuscript of a review article covering the literature through December 20, 1964.

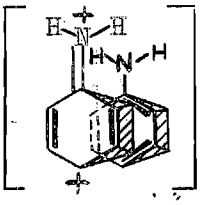
(Π-donor) and electron-poor (Π-acceptor) fragments which are held together by a strong, dative Π-bond is lost.



(Eq. 8)

Furthermore, it is difficult to see how this bonding picture can be useful in predicting the rearrangement products derived from dissymmetric hydrazobenzenes.

Ingold[3] invokes a heterolytic cleavage of the nitrogen-nitrogen bond and postulates that the interaction between the two fragments is electrostatic in nature. He prefers to view the transition state of the two proton mechanism as consisting of an essentially neutral, aniline-like fragment which is held by electrostatic bonding to a di-positively charged fragment which has a quinoid structure as its major contributing resonance structure, (Eq. 9).



(Eq. 9)

Other theories include a diradical intermediate which has been suggested by Večeřa, et al.,[31] and also by Hammond and Clovis,[25] who claim that the vague evidence for the dimerization of the radical cation Wurster's Blue at high concentrations[32] serves as precedent.

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(31) M. Večeřa, L. Synek and V. Štěrba, Coll. Czech. Chem. Comm., 25, 1992 (1960).

(32) K. H. Hausser and J. N. Murrell, J. Chem. Phys., 27, 500 (1957).

However, the lack of e.s.r. signals under conditions which permit the detection of radical concentrations of 10^{-9} molar[3] argue against such a mechanism. Furthermore, Adams et al.,[33,34] have conclusively demonstrated that when N,N-dimethylaniline is anodically oxidized to give N,N,-N',N',-tetramethylbenzidine as the main product, each dimethylaniline molecule that loses any electrons loses two at once to give directly the doubly charged cation, which then reacts with a neutral dimethylaniline molecule to yield the product.

The mechanism suggested by Ferstandig,[35] which involves a transition state composed of a proton π-bonded between the two benzenoid rings (with ferrocene cited as precedent), although novel, has no plausible chemical analogy, and some of the work presented in this thesis provides direct evidence against such a mechanism. For these reasons, this mechanism will not be considered further in this section.

The alternatives which remain in contention are the Ingold polar transition state mechanism[3] and the Dewar π-complex mechanism.[30] Unfortunately, kinetic evidence alone is incapable of distinguishing between these two theories, and more intuitive arguments must be relied upon as the criteria for selection of the most descriptive mechanism.

The Dewar mechanism deals satisfactorily with the strict intramolecularity of the rearrangement by hypothesizing that the nitrogen-nitrogen single bond is replaced by a strong dative π-bond which holds

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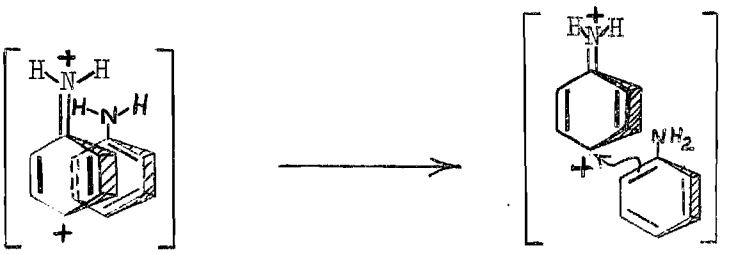
(33) T. Mizoyuchi and R. N. Adams, J. Am. Chem. Soc., 84, 2058 (1962).
(34) Z. Galus and R. N. Adams, J. Am. Chem. Soc., 84, 2061(1962).
(35) L. L. Ferstandig, Tetrahedron Letters, 1963, 1235.

the rings together as the reacting molecule passes through the rate-limiting transition state of the reaction. Dewar describes this Π-bonding as a definite covalent bond, not to be confused with charge transfer complexes or other similar loose associations.[30]

After Π-complex formation has taken place, the products are envisaged to arise from 4,4'-coupling of its initial conformation to yield benzidines. Free rotation of the benzenoid rings about the axis of the dative Π-bond allows the formation of 2,4'-diphenylines and 2,N'-semidines. However, as Ingold has pointed out, it is not clear how such a model can accommodate the observed substituent effects on the course of the rearrangement.

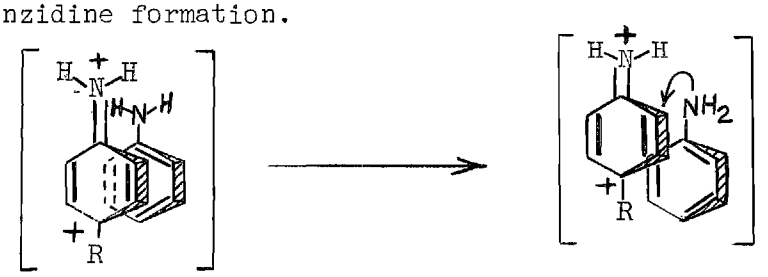
Ingold's polar transition state theory[3] explains the effect of substituents on the course of the reaction by postulating that the electron deficient fragment has either a mono- or dipositively charged quinoid structure, depending upon the kinetic hydrogen ion dependence. If the quinoid fragment is dipositively charged, then the two charges will be situated as far as possible from each other to minimize coulombic repulsive forces within the fragment. As a result, the aniline-like electron-rich fragment will be highly polarized and held to the quinoid fragment by electrostatic interactions. 4,4'-Linkage, where possible, is favored over other modes of linkage. 2,4'-Linkage occurs as a result of slippage of the rings along the plane separating the rings:



(Eq. 10)

Slippage is postulated to be energetically favorable, since it maximizes the electrostatic interaction of the two fragments by bringing the centroids of their charge distributions closer together.

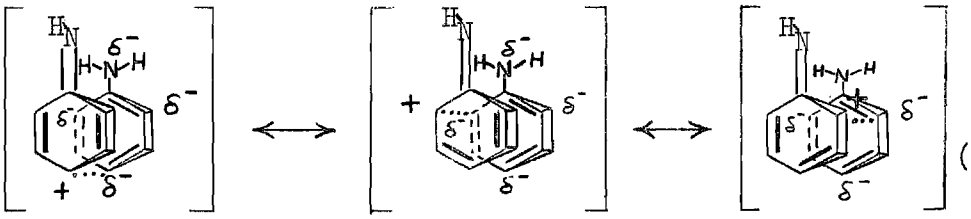
If the rearranging molecule contains a single electron donating substituent in the 4-position, then Ingold's mechanism requires that the dipositively charged fragment contains the substituent, as this will result in the formation of the most stable cation. Then, since electrophilic substitution at nitrogen becomes the most accessable pathway for bond formation, 2,N'-semidine *via* slippage takes place, rather than *ortho*-benzidine formation.



(Eq. 11)

If the 4-substituent is electron withdrawing, then the unsubstituted ring is the precursor of the quinoid fragment and similar reasoning is applied to explain the resulting 2-amino-4'-substituted diphenylamine (semidine).

If rearrangement takes place *via* the one proton mechanism, then the electron deficient fragment contains only a single delocalized positive charge distributed to the *para* and *ortho* positions of the ring in contrast to the highly localized nature of the charges in the two proton mechanism. As a result of this charge distribution, no slippage of the rings is required to maximize the electrostatic interaction between the fragments, and only 2,2'- and 4,4'- linked products result. See Eq. 12 on the following page.



(Eq. 12)

Although Ingold's theory relies heavily on intuitive arguments, it does appear to accommodate the bulk of the known experimental facts, and thus it appears to be the better picture of the transition state bonding in the benzidine rearrangement. Dewar[30] objects to the bonding picture in the Ingold theory and maintains that the electrostatic bonding which Ingold invokes would not be sufficient to impose intramolecularity on the course of the reaction. However, the large entropy advantage that intramolecular processes have over intermolecular processes (assuming that reaction geometries and bond angles are favorable in the transition state) negates Dewar's demand for a strong bonding interaction between the two fragments in the transition state.

Benzidine-like Rearrangements

Beyer, et al.,[36,37] have found examples of benzidine-like rearrangements with 2-phenylhydrazinopyridine, 2-phenylhydrazino-6-methylpyridine, 2,2'-bis-phenylhydrazinobithiazolyl-(4,4') and 2-phenylhydrazinoimidazole. As yet, the intramolecularity of these rearrangements has not been established, but it is very likely that closer examination will confirm the deduction that these are manifestations of the benzidine rearrangement.

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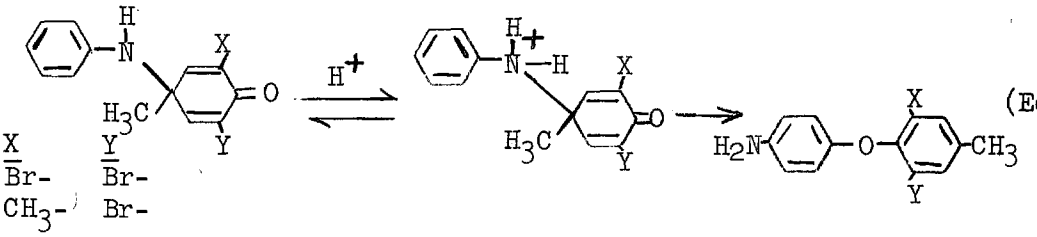
(36) H. Beyer, H. J. Haase and W. Wildgrube, Chem. Ber., 91, 247 (1958).

(37) T. Pyl, H. Lahner and H. Beyer, Chem. Ber., 94, 3217 (1961).

The quinamine rearrangement, the acid-catalyzed rearrangement of substituted 4-arylaminocyclohexadienones to substituted 4-aminodiphenylethers, diphenyls and diphenylamines (Eq. 13), was first discovered by Fries, et al.[38,39] in 1928. Miller[40] has recently investigated the mechanism of this interesting rearrangement, and he has found the rearrangement to be intramolecular and to follow a second-order rate law,



(Eq. 13)

X	Y
Br-	Br-
CH_3-	Br-

first order with respect to quinamine and first order with respect to acid. Miller hypothesizes that the quinamine rearrangement takes place via nitrogen protonation followed by the rupture of the carbon-nitrogen bond. The reacting molecule then passes through a transition state electronically similar to that of the benzidine rearrangement. Miller favors a transition state bonding picture modeled after Dewar's Π-complex theory, but here again, kinetic studies cannot distinguish between the Dewar and the Ingold bonding concepts and the bonding remains a matter of conjecture.

The Mechanism of the Nitramine Rearrangement

In 1894, Bamberger[41] discovered that treatment of aromatic N-nitroamines with concentrated mineral acid catalyzed their conversion to

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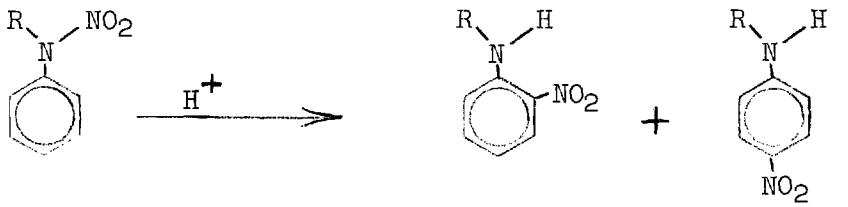
(38) K. Fries and G. Oehmke, Ann., 462, 1 (1928).
(39) K. Fries, R. Boeker and F. Wallbaum, ibid., 509, 73 (1934).
(40) B. Miller, Tetrahedron Letters, 1962, 55 and J. Am. Chem. Soc., 86, 1127, 1135 (1964).
(41) E. Bamberger, Chem. Ber., 27, 584 (1894) and 28, 399 (1895).

aromatic o-nitroanilines as the major product along with traces of the para isomer.



(Eq. 14)

The early work of Holleman, Hartogs and Linden[42] was the first attempt to determine whether or not the rearrangement is intra- or intermolecular. They undertook comparative product studies of the rearrangement and the direct nitration of the corresponding aniline. Bradfield and Orton[43] in 1929, and later Hughes and Jones,[44] refined these product studies, and it was conclusively demonstrated that the product ratios obtained from rearrangement and those obtained from direct nitration are radically different. Table 1 lists the findings of Hughes and Jones on the comparison of the rearrangement of N-nitroaniline with the direct nitration of aniline under similar conditions of acidity.

Table 1. Product Comparison of the Nitration of Aniline and the Rearrangement of N-Nitroaniline[44]

Compound	Yields (per cent) o-	m-	p-
N-nitroaniline (74 per cent aqueous sulfuric acid at -20°)	93	0	7
Anilinium Nitrate (95 per cent aqueous sulfuric acid at -20°)	4	39	56

More recently Hughes, et al.,[45] and Banthorpe, et al.,[46] studied the rearrangement of N-nitroaniline in the presence of nitrogen-15 labeled nitric and nitrous acids and they have shown that the resulting ortho and para nitroanilines contain less than two per cent nitrogen-15 enrichment, thus excluding any intermolecular processes involving NO_2^+, $\cdot NO_2$, NO^+, NO and NO_2^-, since all would be expected to undergo rapid equilibration with either nitrous acid or nitric acid or derived species such as N_2O_5, N_2O_4 or N_2O_3. These experiments firmly establish the intramolecularity of the rearrangement of N-nitroaniline.

Under special circumstances, intermolecular reactions have been observed. Hughes and Jones[44] found that N-methyl-N-nitro-2,4-dinitroaniline, which smoothly undergoes rearrangement under normal conditions, was capable of nitrating p-xylene, phenol or dimethylaniline under rearrangement conditions.

White and Golden[47] have reported that the mixed rearrangement of N-methyl-N-nitroaniline and N-methyl-^{15}N-nitro-p-fluoroaniline results in the formation of isotope nitrogen-15 enriched N-methyl-p-nitroaniline. The extent of nitrogen-15 exchange among the other products of

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(42) A. F. Holleman, J. C. Hartogs, and T. van der Linden, Chem. Ber., 44, 704 (1911).

(43) A. E. Bradfield and K. J. P. Orton, J. Chem. Soc., 1929, 915.

(44) E. D. Hughes and G. T. Jones, J. Chem. Soc., 1950, 2678.

(45) S. Brownstein, C. A. Bunton and E. D. Hughes, J. Chem. Soc., 1956, 4354.

(46) D. V. Banthorpe, J. A. Thomas and D. L. H. Williams, J. Chem. Soc., 1965, 6135.

(47) W. N. White and J. T. Golden, Chem. Ind. (London), 138 (1962).

reaction was not determined. Although this observation suggests the existence of an intermolecular component to the rearrangement, there are formed considerable amounts of N-methylaniline from the rearrangement of N-methyl-N-nitroaniline under the conditions of the labeling experiment (40° and 1 N hydrochloric acid). The labeled cross-product may result from the nitration of N-methylaniline by the labeled N-nitro-p-fluoro material, or it may simply be the result of the displacement of fluorine during the course of the rearrangement, as such processes are known to occur in the benzidine rearrangement. These and other alternatives have been suggested by Banthorpe, et al.[46]

White, et al.,[48] reported that the rearrangement of N-methyl-N-nitroaniline at 40° in 1 N hydrochloric acid yields N-methyl-o-nitroaniline (52.1 per cent), N-methyl-p-nitroaniline (30.9 per cent), N-methylaniline (9.4 per cent) and nitrous acid (13 per cent), but that rearrangement in the presence of a 4-fold excess of hydroquinone decreases the yield of the ortho isomer to 42 per cent and that of the para isomer to 19 per cent without affecting the rate of rearrangement. This suggests that there is formed during rearrangement a reactive intermediate which can be partitioned between hydroquinone and formation of the ortho and para isomers.

Kinetic studies by these same workers[47] on a series of para substituted N-nitroanilines showed the rearrangement to be a second-order reaction, first order in nitramine and first order in the Hammett

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(48) W. N. White, J. R. Klink, D. Lazdins, C. Hathaway, G. T. Golden and H. S. White, J. Am. Chem. Soc., 83, 2024 (1961).

acidity, h_o. The individual rate constants were found to be correlated well by the Hammett $\sigma\rho$ relationship when σ^+ substituent constants were employed. The rearrangement was found to have a large negative ρ value (ρ = -3.9). This suggests that the transition state of the reaction is stabilized by the resonance interaction of electron-donating substituents with the reaction center, and that electron-donating groups facilitate the reaction.

Banthorpe, Hughes and Williams [49] have studied the kinetics of the rearrangement of N-nitroaniline at 0° over a wide range of acidities, and their findings support the first-order dependence on the Hammett acidity. They also found, as did White, et al.,[48] that the rearrangement exhibits a large solvent deuterium isotope effect (k_{D_2O}/k_{H_2O} = 3.3 for N-nitroaniline). Furthermore, 2,3,5,6-tetradeuteration and 2,4,6-trideuteration did not affect the rate of rearrangement of N-nitroaniline, but deuteration did affect the ortho/para product ratio at low acidities, but not at high acidities. 2,3,5,6-Tetradeuteration increased the yield of the para isomer, while 4-deuteration in 2,4,6-trideutero-N-nitroaniline more than offset the effect of the ortho deuteration, resulting in an increase of the ortho isomer. In contrast, White, et al.,[48] could find no substrate deuterium isotope affect on product ratios when deuterated N-methyl-N-nitroaniline was rearranged.

Banthorpe, et al.,[46] also found that the ortho/para ratio was a function of acidity. They found that the relative yields of the ortho

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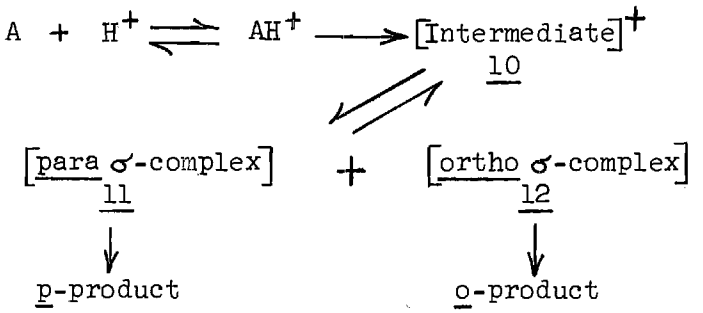
(49) D. V. Banthorpe, E. D. Hughes and D. L. H. William, J. Chem. Soc., 1964, 5349.

and para isomers of N-nitroaniline ranged from 95 to 5 per cent in 74 per cent aqueous sulfuric acid to 70 to 30 per cent in 18 per cent (2.5 molar) aqueous perchloric acid. At concentrations of less than 3 molar and at temperatures above zero degrees, considerable tar formation (up to 40 per cent of total products) was observed.

A thermal nitramine rearrangement has recently been reported by Banthorpe and Thomas[50] for N-methyl-N-nitro-1-naphthylamine, which yields, on heating to 80-100° in a variety of organic solvents, both 2- and 4-nitro-N-methyl-1-naphthylamine.

The preceeding experimental observations on the nitramine rearrangement may be summarized by the following reaction scheme, where A represents an aromatic nitramine.



(Eq. 15)

The driving force for this reaction, as in the benzidine rearrangement, is the replacement of the relatively weak nitrogen-nitrogen single bond in the nitramine by a strong carbon-nitrogen bond in the products. The catalytic function of the proton undoubtedly is to aid in the nitrogen-nitrogen bond cleavage by the inductive electron impoverishment of that bond. The first intermediate, 10, is demanded by the

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(50) D. V. Banthorpe and J. A. Thomas, J. Chem. Soc., 1965, 7158.

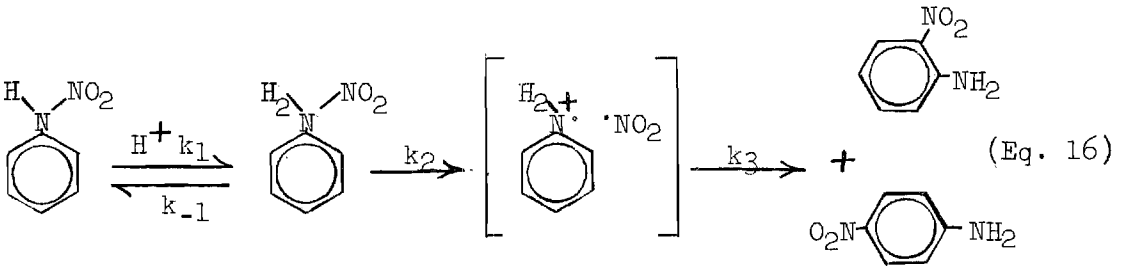
substrate deuterium isotope effect on product ratios in the absence of a measurable kinetic effect,[49] the change in product ratio with acid concentration,[46] and the observation that partition between rearrangement isomers and reaction with hydroquinone takes place without affecting the rate of disappearance of the nitramine.[48] The reversibility of σ-complex formation is demanded by the substrate deuterium isotope effect on product ratios and also by the change in product ratio with acid concentration.

The nature of the first intermediate, 10 , has been the subject of much speculation. Recent theories include the Dewar Π-complex mechanism, the White radical-ion cage mechanism, and the Hughes-Banthorpe cartwheel mechanism.

The Dewar Π-complex mechanism[16,30] envisages the acid-catalyzed conversion of the nitramine to a Π-complex between a neutral aniline fragment and a nitronium ion by protonation of the aniline nitrogen. The Hammett σ_p^+ correlation found be White, et al.,[47] argues strongly against such a picture, as does the identification of nitrous acid rather than nitric acid among the side products in this rearrangement. It appears that there is little if any experimental support for the Dewar Π-complex theory as it is applied to this rearrangement.

White's radical-ion cage theory[48] envisages a protonation of the aniline nitrogen, followed by the homolytic cleavage of the nitrogen-nitrogen bond to give an aniline-radical cation fragment and nitrogen dioxide which then recombine within a solvent cage to form the observed products. Nitrous acid is postulated to occur as a result of nitrogen dioxide escape from the solvent cage followed by reduction to nitrite

ion. The partitioning of the cage intermediate between isomerization and reaction with hydroquinone is cited as evidence for the radical character of the intermediate, although radical products have not been isolated.

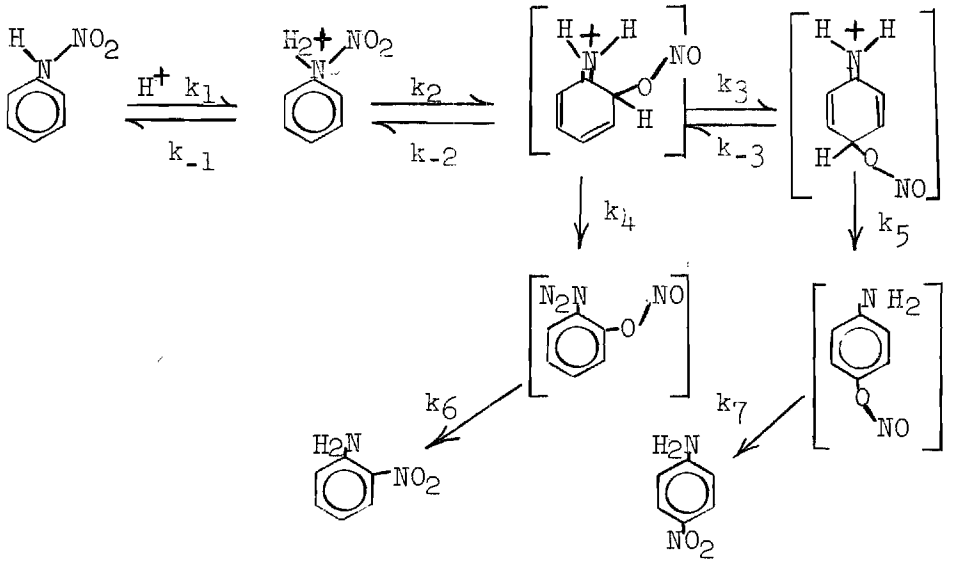


(Eq. 16)

Banthorpe, et al.,[49] point out that reaction with hydroquinone need not occur via a radical process, and they suggest that reaction of hydroquinone with nitrous acid (or an incipient nitrous acid moiety) can account for the experimental observation in question. Indeed, the radical cage mechanism seems to be almost entirely based on this bit of experimental evidence and the observation that under dilute conditions, considerable tar formation accompanies rearrangement. Banthorpe, et al.,[49] have been unable to observe any e.s.r. signals over a wide range of acidities during rearrangement of N-nitroaniline, and thus, any radical pairs which are present must exist in a spin-paired state. It seems far more likely that nitrogen-nitrogen bond cleavage is a heterolytic process.

The Banthorpe-Hughes cartwheel mechanism circumvents the geometrical problem of intramolecularity versus the large intramolecular distances involved in isomerization, by allowing the nitro group of the nitramine, which is protonated on the aniline nitrogen in their picture, to migrate to the ortho position in a Claisen fashion to yield an ortho

nitrite σ-complex as the first intermediate. This intermediate then either migrates again in a Claisen fashion to a para nitrite σ-complex, or it suffers the irreversible loss of the ortho hydrogen as a proton to form an aromatic ortho nitrite which rapidly rearranges to the observed o-nitroaniline. The para nitrite σ-complex reacts in a similar manner to yield the corresponding p-nitroaniline.



(Eq. 17)

The Claisen rearrangement is relied upon heavily for precedent, although examples of para Claisen rearrangements in the presence of an open ortho position are rare and those examples which are known apparently require a strongly electron donating group in the occupied ortho position.[51] The most distressing facet of the Hughes-Banthorpe theory is the unprecedented nitrite to nitro rearrangement. To date no examples of aromatic nitrites are known, although Banthorpe, et al., have attempted to prepare them from the reaction of various phenols with nitrosyl chloride.

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(51) R. C. Fuson, "Advanced Organic Chemistry", first ed., J. Wiley & Sons Inc., London, 1950, pp. 327 ff.

It is clear that existing theories for the mechanism of the nitramine rearrangement are less than satisfactory, and new experimentation is needed to provide the basis for a more satisfactory explanation of this interesting rearrangement.

A Survey of the Chemistry of N-Arylhydroxylamines

Bamberger and coworkers, in their extensive studies of the chemistry of N-phenylhydroxylamine and related compounds, discovered several interesting reactions of this compound and its derivatives which have some bearing on the work presented in this thesis.

In 1894, Bamberger[52] discovered that N-phenylhydroxylamine, when treated with aqueous sulfuric acid yields o- and p-aminophenols. In ethanolic and methanolic solutions, however, the corresponding o- and p-ethoxy and methoxyanilines are the major product, and when hydrochloric acid in aqueous solution is employed, some o- and p-chloroanilines are formed. Furthermore, treatment of N-phenylhydroxylamine with acid in the presence of phenol yields some 4'-hydroxy-4-aminobiphenyl.

The oxygen-18 labeling experiments of Heller, Hughes, and Ingold[53] have demonstrated that the rearrangement of isotopically normal N-phenylhydroxylamine in oxygen-18 enriched water occurs via a completely intermolecular pathway (as Bamberger's product studies indicated), since the resulting phenols contained excess oxygen-18 in the amount expected if rearrangement was accompanied by complete exchange. More recently, it

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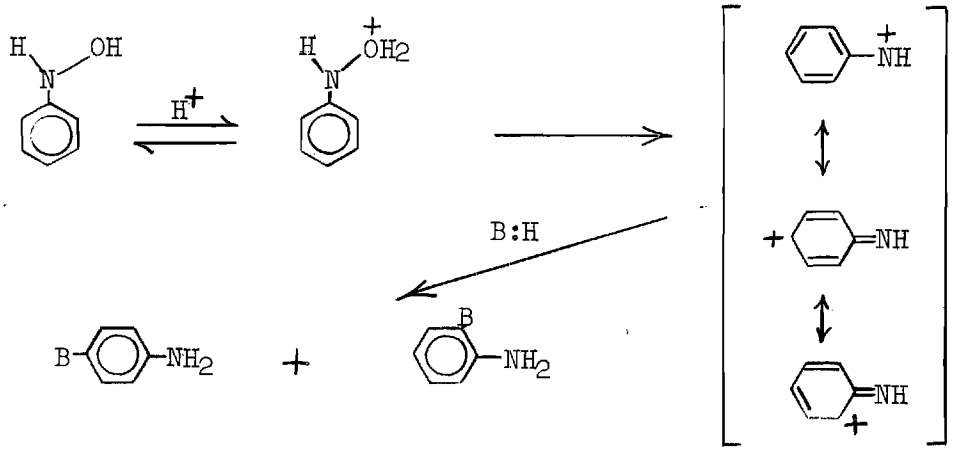
(52) E. Bamberger, Chem. Ber., 27, 1347 and 1548 (1894).
(53) H. E. Heller, E. D. Hughes and C. K. Ingold, Nature, 168, 909 (1951).

has been found that N-ethyl-N-phenylhydroxylamine also undergoes an acid-catalyzed conversion to p-N-ethylaminophenol.[54]

These reactions with the possible exception of the reaction with phenol, are best rationalized on the basis of a modification of Bamberger's original proposal[52] as suggested by Heller, Hughes, and Ingold.[53] They proposed that reaction takes place by protonation of the hydroxylamine oxygen(rather than at nitrogen as Bamberger suggested) followed by loss of water and formation of the resonance stabilized species Ph-NH^+ (as shown in Eq. 18) which reacts with the nucleophiles present in solution. In these equations B:H is the conjugate acid of the attacking nucleophile.



(Eq. 18)

Heller, Hughes and Ingold suggest that loss of water need not proceed by the S_N1 mechanism and they allow for the possibility of an S_N2' attack by the nucleophile at a ring position on the protonated N-phenylhydroxylamine with the simultaneous loss of water from the reacting molecule. Clearly the rate of the S_N2' process should be a function of the

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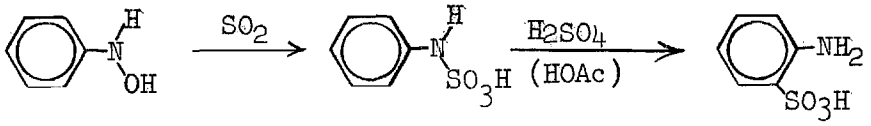
(54) G. Ed. Utzinger and F. A. Regenus, Helv. Chim. Acta, 37, 1885 (1954).

the nucleophilicity of the attacking species. Unfortunately no work (such as kinetic studies) has appeared in the literature to distinguish between the two mechanisms, although Ingold's group promised further studies in this area.

Another interesting rearrangement was discovered by Bamberger and Kunz in 1897.[55] They found that treatment of N-phenylhydroxylamine with sulfur dioxide yields N-phenylsulfamic acid. When this material was then treated with cold concentrated sulfuric acid in glacial acetic acid, there resulted, after several days, a 44 per cent yield of orth-anilic acid.



(Eq. 19)

This interesting transformation almost certainly is an intra-molecular rearrangement, although the mechanism of this reaction has not yet been investigated. The close similarity of this reaction to the nitramine rearrangement has prompted Hughes and Ingold[56] to propose a similar mechanism for it.

In a reaction similar to the reaction of N-phenylhydroxylamine with phenol in aqueous sulfuric acid, Bamberger in 1925,[57] reported that azidobenzene when boiled with phenol in aqueous sulfuric acid

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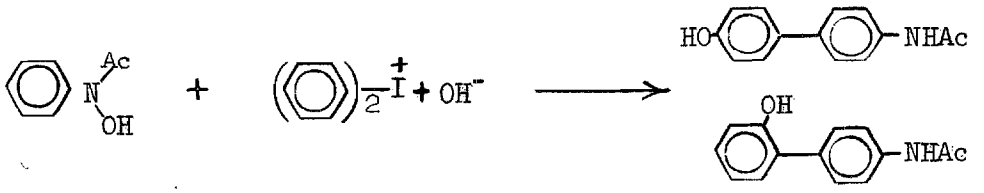
(55) E. Bamberger and J. Kunz, Chem. Ber., 30, 2274 (1897).
(56) E. D. Hughes and C. K. Ingold, Quart. Rev., (London), 6, 34 (1952).
(57) E. Bamberger, Ann., 443, 192 (1925).

yielded the same product, 4'-amino-4-hydroxybiphenyl, and here again reaction is envisaged to proceed via the same electrophilic intermediate $Ph\text{-}NH^{+}$.

In 1963, Dr. James R. Cox, Jr. and I reported[58] evidence for the formation of N-acetyl-O,N-diphenylhydroxylamine, from the reaction of N-acetyl-N-phenylhydroxylamine with diphenyliodonium hydroxide (Eq. 20), as a transient intermediate which spontaneously rearranges under neutral or slightly basic aqueous conditions to 4'-hydroxy-4-acetamidobiphenyl



(Eq. 20)

along with traces of a material thought to be 2'-hydroxy-4-acetamidobiphenyl on the basis of its melting point and infrared spectrum. If this reaction is intramolecular, then the rearrangement may be envisaged to proceed through a transition state similar to that of the benzidine and quinamine rearrangements. This reaction also suggests that Bamberger's acid-catalyzed reactions of N-phenylhydroxylamine and azidobenzene with phenol may involve the intermediacy of O,N-diphenylhydroxylamine which rearranges intramolecularly to the observed product under acid catalysis rather than by direct reaction at the para carbons.

If the rearrangement of the deduced intermediate, N-acetyl-O,N-diphenylhydroxylamine, is indeed a close mechanistic analog of the

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(58) J. R. Cox, Jr. and M. F. Dunn, Tetrahedron Letters, 1963, 985.

benzidine rearrangement, then its study, and the study of related systems, provides a new approach for probing the nature of the transient bonding forces which are operative in the transformation from reactant to products in the benzidine rearrangement. In particular, the N-acetyl substituent further serves to enhance this difference.

The discovery of this reaction has provided the motivation for the work described in this thesis.

CHAPTER III

INSTRUMENTATION AND EQUIPMENT

A modified Hershberg melting point apparatus fitted with a motor driven stirrer and equipped with Anschütz thermometers was used for all melting points below 230° using the open capillary tube method. All melting points and boiling points are uncorrected.

All infrared spectra were taken on the Perkin-Elmer Infracord spectrophotometer using sodium chloride plates, and were calibrated with the 6.238μ band of polystyrene film.

Ultraviolet spectra were obtained on the Cary 14 recording spectrophotometer, and ultraviolet kinetic measurements were obtained on the Zeiss PMQ-II spectrophotometer equipped with a thermostated cell compartment and cell holder.

All n.m.r. spectra were obtained on the Varian Associates Model A-60 spectrometer using tetramethylsilane for both internal and external standardization.

Mass spectra analyses of the carbon dioxide from combusted samples were obtained on the Consolidated-Nier Model 21-103 C mass spectrometer[59] and the Atlas CH-4 mass spectrometer was used for the direct isotopic analysis of various labeled organic compounds.[60] These samples

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(59) We thank Prof. F. H. Westheimer and Dr. G. Dudek of Harvard University for making available their instrument for these measurements.

(60) We thank the University of Illinois and Dr. M. G. Newton for making their instrument available and for assisting in the determination of these spectra.

were introduced by the indirect inlet method at the usual operating temperature.

Standard, ground glass equipment was employed throughout for all syntheses and reactions except for those experiments requiring degassed reaction conditions. The apparatus shown in Fig. 1 was used in these experiments, and its use is discussed in detail with the description of those experiments in the following section.

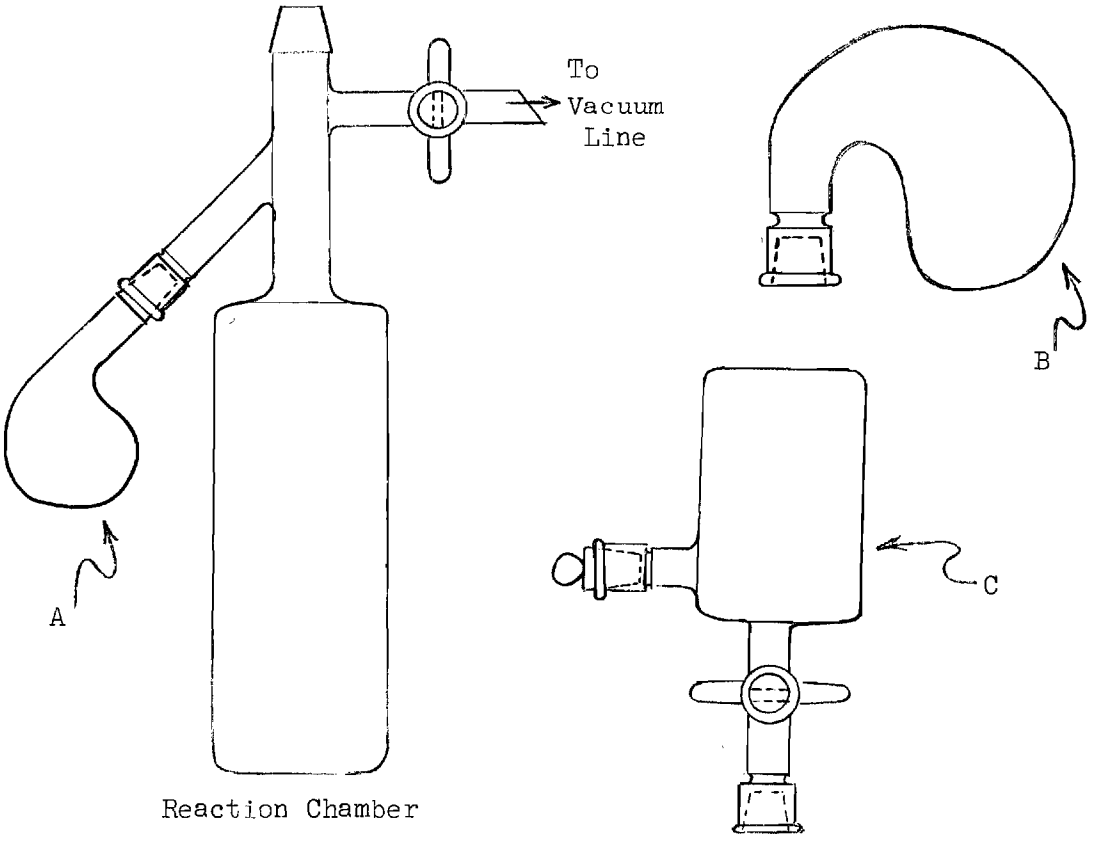

Figure 1. Reaction Degassing Apparatus

CHAPTER IV

SYNTHESIS AND EXPERIMENTS

Iodyl Sulfate

Iodyl sulfate was prepared after the method of Masson and Hanby,[61] by slowly adding iodine, 25.38 g. (0.100 mole), to a vigorously stirred suspension of finely divided potassium iodate, 64.20 g. (0.300 mole), in 160 ml. of concentrated sulfuric acid. The resulting mixture was stirred for 3-4 hrs. until the heterogeneous mixture became a homogeneous bright yellow. The mixture was filtered under aspirator vacuum, yielding iodyl sulfate as a yellow solid which, after washing once with 50 ml. of cold concentrated sulfuric acid and suction drying, was used in the following preparation.

Diphenyliodonium Bisulfate

The following is a modification of Beringer's proceedure[62,63] for diphenyliodonium bisulfate. Iodyl sulfate (in the amount prepared above) was placed in a 500 ml. 3-necked flask and suspended in 75 ml. of concentrated sulfuric acid. The stirred suspension was cooled to 5° in an ice-salt slurry and 75 ml. of freshly distilled acetic anhydride was

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(61) I. Masson and W. E. Hanby, J. Chem. Soc., 1937, 1718.
(62) F. M. Beringer, M. Drexler, E. M. Grindler and C. C. Lumpkin, J. Am. Chem. Soc., 75, 2905 (1953).
(63) F. M. Beringer, R. A. Falk, M. Karniol, I. Lillien, G. Masullo, M. Mausner, E. Sommer, ibid, 81, 342 (1959).

added dropwise to the solution at such a rate that the temperature was maintained below 15°. The resulting heterogeneous mixture was then cooled to 5° and 78.0 g. (1.00 mole) of distilled, thiophene-free, dry benzene was added dropwise to the mixture at such a rate that the temperature did not exceed 10°. The resulting mixture was then allowed to stir overnight, and slowly warm to room temperature. The vessel was tightly stoppered to maintain anhydrous conditions. This resulted in the formation of a homogeneous, caramel-colored viscous solution, which, on careful dilution with approximately 500 ml. of anhydrous ethyl ether (added to a cloud point at room temperature) followed by slow cooling at refrigerator temperatures, yielded 92 g. of a tan, microcrystalline solid which darkened slightly at 155°, melted with decomposition at 167° and finally became a clear amber liquid at 174°. An additional 15.3 g. of the tan material was recovered on further dilution of the mother liquor with 200 ml. of anhydrous ether. The total crude yield of diphenyliodonium bisulfate was 57.5 per cent of theory based on benzene, however, this yield probably represents a minimum value, since the amounts used were based on the assumption that the iodyl sulfate was prepared in quantitative yield.

The crude diphenyliodonium bisulfate was found to be easily purified by first washing with stock acetone, followed by dissolving in methanol and boiling with decolorizing charcoal until the solution gave a colorless filtrate. This solution was then diluted with boiling ether until a cloudy solution was obtained. The cloudy solution was then diluted by the dropwise addition of methanol until clear. Upon cooling,

this solution yielded glistening white needles of the bisulfate which decomposed at 185-187° (reported,[63] dec. 167-169°) to a light yellow liquid.

Isotopic Oxygen-18 Analysis

The mass spectrometer analyses, using a Consolidated-Nier Model 21-103C mass spectrometer, were performed after the method of Rittenburg and Ponticorvo.[64] This method employs mercuric chloride as the combustion catalyst for converting the oxygen in carbon-containing compounds to carbon dioxide. The combustions were carried out at approximately 430° for two hours, and the analyses were performed on the carbon dioxide produced, which was isolated and purified via vacuum manifold manipulations after the technique developed by Haake.[65] Calculations of per cent isotopic oxygen-18 content were based on the ratio of mass peaks at 44 mass units (carbon dioxide $C^{16}O_2$) and 46 mass units ($C^{16}O^{18}O$) obtained directly from the spectrum.

Analyses of samples which were not combusted were carried out on an Atlas CH-4 mass spectrometer by recording the cracking pattern and the detail in the molecular weight region. The per cent oxygen-18 content was estimated[66] by comparing the relative heights of the M and M+2 peaks of the material from the labeling experiments with authentically labeled materials. In some cases, additional information could be

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(64) D. Rittenberg and L. Ponticorvo, Int. J. App. Rad. and Isotopes, 1, 208 (1956).

(65) P. Haake, Ph. D. Thesis, Harvard University (1960).

(66) K. Biemann, "Mass Spectrometry", McGraw-Hill Co., New York, 1962, pp. 204 ff.

obtained from the various fragments in the cracking pattern. It was observed that the N-acetyl derivatives gave intense peaks derived from fragmentation to the corresponding aryl amine and ketene, and thus a check on the oxygen-18 content of the aryl amine fragment could be obtained by comparing the height of this peak with the peak which was two mass units higher. The sample of dichloroacetic acid enriched with oxygen-18 was found to fragment to carbon dioxide and methylene chloride as well as other fragments, and the oxygen-18 content was estimated by comparison of the peaks at mass 44 and 46. It was found that direct measurements on the purified organic materials gave oxygen-18 isotope ratios which were generally less accurate than those obtained from the analysis of the carbon dioxide from combusted samples.

N-Acetyl-N-phenylhydroxylamine

Freshly distilled acetic anhydride, 102 g. (1.00 mole), was added dropwise to a stirred solution of N-phenylhydroxylamine, 109.4 g. (1.00 mole), dissolved in 300 ml. of ethyl ether cooled in a salt-ice slurry, at such a rate that the temperature of the reaction mixture was maintained below 0°. The reaction mixture was stirred for an additional three hrs. at 0° and then evaporated at ambient temperature to an amber, viscous residue by means of a rotary evaporator under aspirator vacuum. This residue was further evaporated at ambient temperature under 0.05 mm. vacuum to a crystalline mass which was collected by vacuum filtration, yielding after one recrystallization from hot carbon tetrachloride 77.45 g. (51 per cent of the theoretical amount) or N-acetyl-N-phenylhydroxylamine. A second recrystallization from carbon tetrachloride

after boiling with decolorizing charcoal gave glistening, colorless prisms, m.p. 66.5-67.5° (reported,[67] m.p. 67°).

Authentic 4'-Hydroxy-^{18}O-4-acetamidobiphenyl

N-Acetylbenzidine,[68] 8.95 g. (0.0396 mole), was dissolved in approximately 200 ml. of acetone followed by the addition of 19.4 g. of approximately 50 per cent tetrafluoboric acid solution (J. T. Baker's Analyzed Reagent), which precipitated the amine as its tetrafluoborate salt. The resulting slurry was cooled to and maintained at -5° in an ice-salt bath while 3.72 g. (0.0361 mole) of n-butylnitrite was added dropwise to the mixture under vigorous stirring. Upon completion of addition, the formation of a yellow precipitate of the diazonium salt was observed. The mixture was stirred for one hr. at 0° and then the diazonium salt was isolated by vacuum filtration and was washed with acetone. The diazonium salt, 2.00 g. (0.00615 mole), was added to a solution of oxygen-18 enriched (1.51 atom per cent enrichment) deuterium oxide (purchased from YEDA Research and Development Co. Ltd.), made slightly acidic by bubbling dry hydrogen chloride through the solution for two or three min. The mixture was then heated for two hrs. at 70-80° with loss of nitrogen evidenced by the evolution of gas bubbles from the mixture. After gas evolution could no longer be observed, the solution was heated to 90° for 30 min. The mixture was then cooled and the brown insoluble reaction product was isolated by vacuum filtration.

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(67) E. Bamberger, Chem. Ber., 51, 637 (1918).
(68) H. Schmidt and G. Schultz, Chem. Ber., 12, 487 (1879).

This material was sublimed at 180-190°/0.05 mm., yielding, after two sublimations, a light yellow (almost white) solid, m.p. 224-226°, which recrystallized from hot ethanol as a white solid, m.p. 225-226°, of which melting was not depressed by admixture with authentic 4'-hydroxy-4-acetamidobiphenyl prepared by the method of Bamberger.[69] The material gave an infrared spectrum superimposable with that of the authentic material. The yield of the purified material was 0.42 g., 30 per cent of the theoretical amount. The mass spectrum of a sublimed sample of this material gave an M+2 peak (mass 229) which was 3.30 per cent of the intensity of its parent peak (mass 227), while an isotopically normal sample gave an M+2 peak intensity which was 1.70 per cent of the intensity of its parent peak. This corresponds to an oxygen-18 enrichment of 1.57per cent, in good agreement with the expected value of 1.51 per cent.

Authentic Phenol Labeled with Isotopic Oxygen-18

Benzenediazonium tetrafluoborate, 10.3 g. (0.0567 mole), was added to a 100 ml. flask containing 50 ml. of deuterium oxide enriched in isotopic oxygen-18 (1.51 atom per cent purchased from YEDA Research and Development Co. Ltd.) and three drops of concentrated sulfuric acid. The mixture was heated at 60-70° until the evolution of nitrogen ceased. The mixture was then saturated with sodium chloride and extracted with ether. The ether extract was evaporated under reduced pressure at room temperature, and the phenol residue (reddish tint) was distilled under vacuum, yielding 3.01 g. (0.034 mole) of phenol enriched in isotopic

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(69) E. Bamberger, Ann., 443, 196 (1925).

oxygen-18 content which crystallized as a colorless solid. The mass spectrum of this material indicated it contained the expected amount of oxygen-18.

The Reaction of Diphenyliodonium Ion with N-Acetyl-N-phenylhydroxylamine in Oxygen-18 Enriched Deuterium Oxide Solvent

Diphenyliodonium bisulfate, 3.800 g. (0.0100 mole), was placed in the reaction degassing apparatus (Fig. 1) and N-acetyl-N-phenylhydroxylamine, 1.512 g. (0.0100 mole), was placed in side arm (A) of the apparatus. Deuterium oxide, 30 ml. enriched with isotopic oxygen-18 (1.51 atom per cent purchased from YEDA Research and Development Co.,Ltd.), was added to the flack followed by the addition of 20 ml. of 1.00 normal NaOd-D_2O (oxygen-18 enriched) solution. The 1.00 normal solution was prepared from the reaction of the enriched deuterium oxide with a commercially available sodium-lead alloy (J. T. Baker's dri-Na analyzed at 9.6 per cent active sodium) to avoid contamination. The resulting solution was degassed by freezing and thawing in a Dry Ice-acetone slurry through 4 cycles under 0.25 mm. The degassed solution was then warmed to room temperature and mixed with the N-acetylphenylhydroxylamine contained in the side arm of the apparatus. Upon being mixed, the solution immediately acquired a light yellow color and then darkened. After 30 min. a dark brown, viscous oil began to separate and cling to the sides of the apparatus. After 42 hrs. at room temperature the aqueous portion of the reaction mixture was decanted from the insoluble products, which remained on the walls of the reaction apparatus. The filtrate was found to be slightly basic (pH 8) to pH paper. Treatment of the filtrate

with sodium bromide gave a precipitate of diphenyliodonium bromide in an amount corresponding to 6.93 per cent of the starting material. The water insoluble reaction products left on the walls of the apparatus were dried under high vacuum for three hrs. and then washed with 20 ml. of chloroform, yielding 0.76 g. (33.5 per cent of theory) of a tan residue, m.p. 225-226°, which recrystallized from hot ethanol as a microcrystalline white powder, m.p. 226-227°, which did not depress the melting point of authentic 4'-hydroxy-4-acetamidobiphenyl (reported,[70] m.p. 225-226°), upon admixture. The two materials also exhibited superimposable infrared spectra. The O,N-diacetyl derivative, m.p. 220-222°, was similarly compared with authentic material as was the hydrolysis product 4'-hydroxy-4-aminobiphenyl, dec. 260-265° (reported,[70] dec. 270°). Both derivatives exhibited no depression of melting point (or dec. point) on admixture, and both were found to exhibit infrared spectra superimposable with authentic materials. Mass spectrometric analysis of the carbon dioxide from a combusted sample of the reaction product indicated that the material contained no more than the natural abundance of oxygen-18 (found: 0.204 per cent, natural abundance: 0.20 per cent). It has been found that fractional recrystallization or column chromatography[71] of the chloroform soluble portion of the reaction products over neutral alumina yields, with difficulty, small amounts (8-10 per cent) of a second material which is thought to be 2'-hydroxy-4-acetamidobiphenyl on

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(70) L. C. Raiford and E. P. Clark, J. Am. Chem. Soc., 48, 483 (1925).

(71) M. F. Dunn, "The Chemistry of O,N-Diarylhydroxylamines", a thesis presented in partial fulfillment of the requirements for the Master of Science Degree, Georgia Institute of Technology, 1963.

the basis of its melting point, m.p. 197-198° (reported,[72] m.p. 198-199°), and the similarity of its infrared spectrum to that of the 4' isomer. In other runs, up to 40 per cent of the theoretical amount of iodobenzene has been recovered from the reaction mixture by trapping the liquid in a Dry Ice-acetone trap on a high vacuum line during the work-up proceedure.

The Reaction of Diphenyliodonium Ion with N-Acetyl-N-phenylhydroxylamine in the Presence of Phenol-^{18}O

The procedure for this experiment was identical with the previously described phenylation reaction except that the isotopically normal aqueous sodium hydroxide solution contained phenol (enriched with 1.51 atom per cent oxygen-18) in a molar ratio of 1:1. The diphenyliodonium bisulfate and the N-acetyl-N-phenylhydroxylamine were placed in side bulbs A and B (Fig. 1) prior to degassing and mixing. Mixing was accomplished by first dissolving the N-acetyl-N-phenylhydroxylamine and then the diphenyliodonium bisulfate. After the resulting reaction mixture had stood at room temperature for 20 hrs., the aqueous portion was removed by decanting from the residues clinging to the walls of the apparatus. The residues were vacuum dried, yielding a reddish-brown amorphous residue. The Dry Ice trap yielded 1.30 ml. of iodobenzene. Treatment of the aqueous filtrate with sodium bromide gave a precipitate of diphenyliodonium bromide in a yield of 8.5 per cent of the starting amount of diphenyliodonium bisulfate. The dried residue in the reaction

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(72) C. Finzi, Gazz. chim. Ital., 61, 33 (1931).

apparatus was washed with chloroform, yielding 4'-hydroxy-4-acetamidobiphenyl as a light tan solid, m.p. 223-226°, in a crude yield of 40 per cent of the theoretical amount (corrected for the amount of unreacted diphenyliodonium ion). Approximately 0.2 g. of this material was washed with ether, then acetone and again with chloroform, yielding a white, microcrystalline material which sublimed at 180°/0.05 mm., yielding a glistening white sublimate, m.p. 226.0-227.5°. This material was found to be identical with authentic 4'-hydroxy-4-acetamidobiphenyl by mixed melting point, which was undepressed, and by the comparison of infrared spectra, which were superimposable. The mass spectrum of a sublimed sample of this material gave an M+2 peak (mass 229) intensity which was 1.66 per cent of the intensity of its parent peak (mass 227), while an isotopically normal sample and an authentically labeled sample (enriched with 1.51 per cent oxygen-18 in the phenolic oxygen) gave M+2 peak intensities which were respectively 1.70 per cent and 3.30 per cent of the intensities of their corresponding parent peaks. Thus the material from this labeling experiment contains no oxygen-18 in excess of the natural abundance (0.20 per cent).

Perchloric Acid-d_1

Pure deuteroperchloric acid was prepared by the method of Brauer[73] by the reaction of concentrated sulfuric acid-d_2 (99.6 atom per cent deuterium) with anhydrous sodium perchlorate.

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(73) S. Brauer, "Handbuch der Präparativen Anorganischen Chemie", Enbe, Stuttgart, pp. 290 (1951).

The resulting concentrated acid was diluted with the necessary amount of deuterium oxide (99.8 atom per cent deuterium) to yield a 6.00 N deuteroperchloric acid solution. Comparison of the n.m.r. of a sample of this solution with an authentic sample of 99.8 per cent deuterium oxide indicated that it had an approximate deuterium content of 99.7-99.8 per cent.

N-Acetylhydrazobenzene

N-Acetylhydrazobenzene was found to be conveniently prepared by treatment of hydrazobenzene with excess acetic anhydride after the method of Goldschmidt and Euler.[74] The crude reaction product, obtained in almost quantitative yield, recrystallized from hot ligroin as glistening, white needles, m.p. 161-162.5°. Further recrystallization from chloroform yielded material melting at 162-163° (reported,[74] 159°).

2,3,4,5,6,2',3',4',5',6'-Decadeutero-N-acetylhydrazobenzene

Perdeutero-N-acetylhydrazobenzene was prepared by the nitration of benzene-d_6 (99.5 atom per cent deuterium content purchased from Merck, Sharpe and Dohme of Canada, Ltd.) with nitric acid-d_1 and sulfuric acid-d_2 (99.5 atom per cent deuterium) followed by reduction of the resulting nitrobenzene-d_5 (shown to contain 99.5 atom per cent deuterium by n.m.r.) with zinc dust in alcoholic sodium hydroxide, and finally acylation with acetic anhydride. The nitration, reduction and acylation steps resulted in crude yields of 76.5, 75.5 and 86.0 per cent of the theoretical

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(74) S. Goldschmidt and K. Euler, Chem. Ber., 55, 616 (1922).

amounts respectively. The resulting N-acetylhydrazobenzene, m.p. 162-163°, gave an n.m.r. spectrum which indicated that the aromatic rings are highly deuterated, although no quantitative data could be obtained due to the chemical shift of the N-H proton (δ = 6.96 relative to tetramethylsilane as an external standard), which places it directly over the aromatic region. The infrared spectrum of this material also indicated that the rings were highly deuterated.

The Acid-catalyzed Reaction of N-Acetylhydrazobenzene in Ethanol-water Solution

When 1.00 g. (0.00487 mole) of N-acetylhydrazobenzene was dissolved in 75 ml. of absolute ethanol (or methanol) followed by the slow addition of 10 ml. of concentrated hydrochloric acid, and the resulting solution allowed to stand at room temperature, there was formed after six hrs. a white, crystalline material. After 24 hrs. the accumulated crystalline material was collected by vacuum filtration, redissolved in water and neutralized by adjusting the pH to about 8 by the addition of dilute sodium hydroxide. This treatment precipitated 0.55 g. of a soft, white solid which was collected by extraction with ether followed by evaporation of the ether extract under reduced pressure, yielding a glistening, almost white solid, m.p. 123-124°, which exhibited an infrared spectrum superimposable with that of authentic benzidine; yield 62 per cent of theory.

The Rearrangement of N-Acetylhydrazobenzene Under Concentrated Aqueous Acid Conditions

Treatment of 1.00 g. of N-acetylhydrazobenzene with 10 ml. of 60

per cent perchloric acid yielded immediately a dark greenish-brown solution accompanied by the evolution of considerable amounts of heat. After 30 min., the solution was cooled in ice and neutralized with dilute sodium hydroxide, affording an insoluble, tan solid material which was collected by vacuum filtration and vacuum dried, yielding 0.83 g. (83 per cent of the theoretical amount) or N-acetylbenzidine which decomposed at 195-200°. Recrystallization of this material from hot ethanol yielded an almost white, crystalline material, dec. 202-203° (reported,[68] dec. 199°) which was shown to be identical with N-acetylbenzidine by mixed decomposition point, which was undepressed, and by comparison of infrared spectra, which were superimposable.

Ether extraction of the aqueous filtrate followed by evaporation of the extract at room temperature under reduced pressure yielded approximately 0.1 g. of an oily, brown residue which was not identified.

The Mixed Rearrangement of 2,3,4,5,6,2',3',4',5',6'-Decadeutero-N-acetylhydrazobenzene and Normal N-Acetylhydrazobenzene in 6.01 F Perchloric Acid

N-Acetylhydrazobenzene, 0.1000 g. (0.00043 mole), and perdeutero-N-acetylhydrazobenzene, 0.1394 g. (0.000591 mole), as finely ground powders, were thoroughly mixed and then added to a 50 ml. round bottom flask containing 25 ml. of 6.01 F perchloric acid. Solution was accomplished by placing small amounts of the mixture on the surface of the 19/38 joint of the flask and mulling with 6.01 F perchloric acid by grinding a stopper in the joint, and then washing the resulting mull into the flask with more perchloric acid. This procedure was used for

dissolving the N-acetylhydrazobenzenes, since otherwise there is a marked tendency for the material to form cakes which do not dissolve readily in the acid media. Addition was completed in 15 min. and the resulting reaction mixture was shaken for 80 min. at room temperature. During this time, the formation of N-acetylbenzidinium perchlorate, which is highly insoluble, was observed. The salt, as small light green crystals, was isolated by vacuum filtration of the reaction mixture through a sintered glass funnel. The isolated salt was dispersed in 25 ml. of distilled water and neutralized with anhydrous sodium carbonate. The precipitated N-acetylbenzidine was recovered by vacuum filtration, yielding, after vacuum drying, 0.1840 g. (77 per cent of the theoretical amount) of light yellow material, m.p. 204.5-206.5°. This material was recrystallized from methanol once and sublimed at 160-170°/0.05 mm., yielding soft fine white crystals (as star clusters), m.p. 205.4-206.4°. Analysis of the mass spectrum of this material gave peak intensity ratios of 348 : 0.75 : 498 for the peaks of mass 226, 230 and 234, indicating that not more than 0.20 per cent of the mixed product (mass 230) was formed.

Ring deuterated N-acetylhydrazobenzene, by itself, was rearranged under the same conditions, yielding on workup 91.5 per cent of the crude rearranged material. Analysis of the mass spectrum of this material gave a ratio of peak intensities of 8 : 675 for the peaks of mass 233 and 234 respectively, indicating that the rearranged material contained at least 98.8 per cent ring deuterium.

Rate Studies in 30 Per Cent Methanol-Water Solutions

The kinetics of the conversion of N-acetylhydrazobenzene to benzidine were studied in 30 per cent methanol-water solutions of perchloric acid maintained at a constant ionic strength of 1.08 with added sodium perchlorate. Rate measurements were made by following the change in optical density at 235 mμ (the absorption maximum for N-acetylhydrazobenzene) and at 280 mμ (the absorption maximum for benzidine) of neutralized aliquots withdrawn at various time intervals. The solutions were prepared by placing the required amount of N-acetylhydrazobenzene and sodium perchlorate in a 250 ml. volumetric flask, followed by the addition of 75 ml. of methanol previously distilled over magnesium methoxide. The solution was then added to the flask and the contents were then diluted to a total volume of 250 ml. and thermostated at $30.0 \pm 0.1^{\circ}$. The runs at $60.0 \pm 0.1^{\circ}$ were carried out in a similar manner.

Rate measurements on the solvolysis of N-acetylbenzidine were carried out by following the change in the optical density at 268 mμ (the absorption maximum for N-acetylbenzidinium ion) on aliquots of the acidic solution.

Rate Studies in Aqueous Concentrated Perchloric Acid-Sodium Perchlorate Solutions

Concentrated perchloric acid with a total ionic strength of 6.0 was prepared by the addition of the appropriate amounts of a concentrated standardized perchloric acid solution to 50 ml. volumetric flasks, followed by the addition of the necessary amounts of sodium perchlorate. The resulting solution was then diluted to the calibration mark with

distilled water. Individual kinetic runs were then prepared from these solutions by adding 2-3 mg. of N-acetylhydrazobenzene to a 5 ml. aliquot of the stock solution in a 10 ml. glass stoppered flask. After shaking vigorously for 20 sec., the quartz cell was filled from a capillary eye dropper to avoid including any undissolved particles of the substrate. The filled cell was then placed in the thermostated cell holder of a Zeiss PMQ-II spectrophotometer where rate measurements were made by observing the increase in absorbance at a wave length of 268 mμ (the absorption maximum of N-acetylbenzidinium ion, ϵ_m = 18,400) as a function of time. The cell holder and cell compartment were thermostated at a temperature of 30.0±0.1°. An isosbestic point was found at a wavelength of 236.6 mμ. The absorbance readings at this wavelength were found to be invariant during the course of a kinetic run, while readings 0.5 mμ to either side of this wavelength were found to change with time. No evidence could be found for formation of products other than N-acetylbenzidine in these solutions during the period of time required to complete the kinetic runs, although prolonged observations at 268 mμ indicated that the product is slowly hydrolyzed.

The extinction coefficient of N-acetylhydrazobenzene at its absorption maximum (λ_m = 235 mμ, ϵ_m = 15,600) in 6.00 F sodium perchlorate was found to be unchanged by dilution with the necessary amount of 6.01 F perchloric acid to result in a 4.00 F perchloric acid 2.00 F sodium perchlorate solution, indicating that N-acetylhydrazobenzene is not protonated to any appreciable extent under these conditions.

O,N-Diacetyl-N-phenylhydroxylamine[75]

N-Acetyl-N-phenylhydroxylamine, 3.00 g. (0.02 mole), was dissolved in 10 ml. of acetic anhydride and allowed to stand at room temperature for three hrs. The excess acetic anhydride was removed at room temperature by evaporation under 0.05 mm. vacuum, yielding a light purple, fluid residue which solidified to a purple, crystalline mass on cooling in the refrigerator. Recrystallization from 100 ml. of hot ligroin gave 1.48 g. of glistening white crystals, m.p. 43.5-45.5° (reported,[75] m.p. 43°).

The material exhibited the following n.m.r. absorptions (relative to tetramethylsilane as an external standard) and relative areas: singlet δ = 1.90 (3), singlet δ = 2.06 (3) and a multiplet δ = 7.36 (5). The infrared spectra exhibited characteristic absorptions at 1788 cm^{-1} (O-acetyl carbonyl) and 1671 cm^{-1} (N-acetyl carbonyl) and a lack of absorption in the 4,000 to 3,000 cm^{-1} region. These spectral data confirm the original structural assignment made by Bamberger[75] on the basis of the material's chemical behavior.

O-p-Nitrobenzoyl-N-acetyl-N-phenylhydroxylamine

N-Acetyl-N-phenylhydroxylamine, 1.51 g. (0.01 mole), was dissolved in 40 ml. acetone. Sodium hydroxide, 0.40 g. (0.01 mole), dissolved in 5 ml. water was added to the acetone solution, and the resulting solution was added dropwise to a magnetically stirred solution of

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(75) E. Bamberger, Chem. Ber., 51, 636 (1918).

p-nitrobenzoyl chloride dissolved in 25 ml. of acetone maintained at 0° in a salt-ice slurry. When the addition was complete, there was formed a light yellow precipitate. Addition of 100 ml. water precipitated more yellow material which was collected by vacuum filtration, yielding, after vacuum drying, 2.40 g. of light yellow material, m.p. 135.5-137.5°. This material was assigned the structure O-p-nitrobenzoyl-N-acetyl-N-phenylhydroxylamine on the basis of its infrared spectrum (nujol) which exhibited no absorbance in the 4,000 to 3,000 cm^{-1}. region and strong absorptions at 1775 cm^{-1}. (O-benzoyl carbonyl) and 1715 cm^{-1}. (N-acetyl carbonyl), and on the basis of its n.m.r. spectra which exhibited the following absorptions and relative areas: singlet δ = 2.16 (3), multiplet δ = 7.54 (5) and a singlet δ = 8.34 (4).

No n.m.r. evidence could be found for the rearrangement of this material on treatment with trifluoroacetic acid or dichloroacetic acid at 40° for extended periods of time. Prolonged treatment with these acids appeared to induce a slow decomposition.

The Reaction of N-Acetyl-N-phenylhydroxylamine with p-Toluenesulfonyl Chloride

This reaction was found to be best carried out in the absence of atmospheric oxygen to reduce the formation of decomposition products.

Acetone, 140 ml., was degassed and introduced into the large chamber of the reaction degassing apparatus (Fig. 1) containing p-toluenesulfonyl chloride, 1.91 g. (0.01 mole), by bulb to bulb distillation under 0.05 mm. vacuum. The resulting solution was cooled to approximately -5° in a salt-ice slurry. A previously degassed aqueous solution of

N-acetyl-N-phenylhydroxylamine, 1.51 g. (0.01 mole), and sodium hydroxide, 0.47 g. (0.0117 mole), was then introduced to the cooled, magnetically stirred acetone solution by dropwise addition from the attached flask C (see Fig. 1). When the addition was complete, there was observed a small amount of insoluble, white, crystalline material (which was later found to be sodium chloride) which precipitated from the light pink, aqueous-acetone solution. After two hrs. of stirring, during which the reaction mixture warmed up to room temperature, the contents of the apparatus were transferred to a magnetically stirred, 250 ml., round bottom flask and the solvent was evaporated at room temperature under 0.05 mm. vacuum, into a Dry Ice trap. The resulting off-white residue remaining in the flask was washed with water, collected by vacuum filtration and dried under high vacuum, yielding 2.210 g. of an off-white solid material, m.p. 121-132°. Recrystallization from boiling carbon tetrachloride yielded 2.18 g. of a light tan, almost white material m.p. 130.5-133°. This material was then recrystallized from boiling benzene and a first fraction was recovered by cooling to room temperature and decanting the mother liquor from the water white prisms, m.p. 133-136 °, which adhered to the sides of the recrystallization flask; yield 0.834 g. When the benzene mother liquor was cooled in the freezer and allowed to stand overnight, there was formed a second crop of crystals, a mixture of water white prisms and small, amber prisms. The colorless prisms were separated from the amber prisms by mechanically picking the crystals apart, yielding 0.900 g. of water white prisms, m.p. 132-136°, and 0.142 g. of amber prisms, m.p. 143-147.5°. Evaporation, combination

and recrystallization of mother liquor residues from benzene, yielded 0.211 g. more of the white prisms, m.p. 132-135°, and 0.075 g. more of amber prisms, m.p. 141-146°.

The colorless prisms, m.p. 133-136°, were shown to be identical with authentic o-acetamidophenyl tosylate by mixed melting point, which was undepressed, and comparison of infrared and n.m.r. spectra, which were superimposable. Elemental analysis of this material gave the following values: calculated for $C_{15}H_{15}NO_4S$; C, 59.02; H, 4.95; N, 4.59; S, 10.48. Found: C, 59.02; H, 4.85; N, 4.52; S, 10.56. The total recrystallized yield of this material was 63 per cent.

The amber prisms, m.p. 143-147.5°, were shown to be identical with authentic p-acetamidophenyl tosylate (reported,[76] m.p. 145.5-146°) by mixed melting point, which was undepressed, and by comparison of infrared spectra, which were superimposable. Total yield of this material was 7.1 per cent.

Ether extraction of the aqueous-acetone filtrate yielded a white solid residue which partially dissolved in acetone. The acetone insoluble material gave a white precipitate with silver nitrate and appears to be sodium chloride. Evaporation of the acetone wash yielded 0.295 g. of a white material which appears to be sodium p-toluene sulfonate, as its n.m.r. spectrum (D_2O) was found to be identical with that of an authentic sample. The yield of this material accounted for 15.5 per cent of the starting p-toluene sulfonyl chloride.

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(76) E. Bamberger and A. Rising, Chem. Ber., 34, 228 (1901).

The Reaction of N-Acetyl-N-phenylhydroxylamine with Methanesulfonyl Chloride

A solution of N-acetyl-N-phenylhydroxylamine, 1.51 g. (0.01 mole), dissolved in 20 ml. of acetone and mixed with sodium hydroxide, 0.42 g. (0.01 mole), dissolved in 10 ml. of water was added dropwise over a 15 min. period to a magnetically stirred solution of methanesulfonyl chloride, 1.15 g. (0.01 mole), dissolved in 50 ml. of acetone cooled to 0° in a salt-ice slurry. The resulting reaction mixture was stirred for one hr., followed by the removal of the aqueous-acetone solvent at room temperature under 0.05 mm. vacuum. The resulting white residue was washed with water, yielding, after vacuum drying, 0.48 g. of soft, glistening white material, m.p. 113.5-117.5°. The infrared spectrum (nujol) of this material exhibited a band at 3,360 cm^{-1}., indicating the presence of an N-H group. This material was shown to be identical with an authentic sample of o-acetamidophenylmethane sulfonate by mixed melting point, which was undepressed, and by comparison of infrared spectra which were superimposable.

An n.m.r. study of the reaction of N-acetyl-N-phenylhydroxylamine with methanesulfonyl chloride in carbon tetrachloride catalyzed by triethylamine (no reaction was observed in the absence of triethylamine) indicated that some of the para isomer (estimated to be present in approximately 18 per cent) as well as the ortho isomer was formed in the reaction. However, the para isomer has not been isolated from these reactions.

The Reaction of N-Acetyl-N-phenylhydroxylamine with Trifluoroacetic Anhydride in the Presence of Triethylamine

N-Acetyl-N-phenylhydroxylamine, 1.51 g. (0.01 mole), previously dried under 0.01 mm. vacuum was placed in an oven-dried, 3-necked, round bottom flask and dissolved in 40 ml. of carbon tetrachloride which was freshly distilled over phosphorous pentoxide. Triethylamine, 1.01 g. (0101 mole), freshly distilled from barium oxide, was added to the carbon tetrachloride solution. The resulting solution was cooled to 0° in a salt-ice slurry and trifluoroacetic anhydride, 2.10 g. (0.01 mole), dissolved in 10 ml. of carbon tetrachloride was added dropwise to the stoppered flask from a pressure equalizing dropping funnel over a 15 min. interval. After addition was complete, the resulting amber solution was stirred for an additional hr. at 0° and then for one hr. while the mixture warmed to room temperature. The carbon tetrachloride solvent was then removed at room temperature by bulb to bulb distillation under 0.05 mm. vacuum. After evaporation, there remained in the reaction flask a mobile, light yellow-orange liquid which did not crystallize on prolonged standing at freezer temperatures. The initial infrared spectrum (neat) of this material exhibited an absorption between 3,000 and 4,000 cm^{-1}. at 3,030 cm^{-1}. However, after two days at room temperature this material exhibited a new absorbance in the infrared at 3,505 cm^{-1}. Hydrolysis of a portion of this latter liquid reaction mixture with aqueous sodium hydroxide followed by neutralization to pH 7, yielded a tan material, m.p. 202-203°, which was found to be identical to o-hydroxyacetanilide by mixed melting point, which was undepressed, and by comparison of infrared spectra, which were superimposable.

The Thermal Rearrangement of O-Trifluoroacetyl-N-acetyl-N-phenylhydroxylamine

Vacuum distillation of the freshly prepared reaction mixture of N-acetyl-N-phenylhydroxylamine and trifluoroacetic anhydride in the presence of triethylamine at 101-111°/0.08 mm., yielded a light yellow, almost colorless distillate which, when hydrolyzed with aqueous sodium hydroxide followed by neutralization to pH 7, yielded a yellow-tan crystalline solid, m.p. 202-203°. This material was found to be identical with authentic o-hydroxyacetanilide by mixed melting point, which was undepressed, and by comparison of infrared spectra, which were superimposable. The distilled oil exhibited an n.m.r. spectrum identical with that of the undistilled material which had been allowed to stand at room temperature for two or more days. The n.m.r. spectrum of the distilled material indicated the presence of approximately 13 per cent triethylammonium ion(as the trifluoroacetate ?) which apparently co-distilled.

An N.M.R. Study of the Reaction of N-Acetyl-N-phenylhydroxylamine with Trifluoroacetic Anhydride

An n.m.r. sample of N-acetyl-N-phenylhydroxylamine dissolved in carbon tetrachloride was treated with excess trifluoroacetic anhydride at room temperature, and the n.m.r. spectrum of the resulting reaction mixture was observed over a period of time. The initial spectrum exhibited sharp singlets for both the acetyl methyl proton signal (δ = 2.06 relative to tetramethylsilane as an external standard) and the aromatic proton signal (δ = 7.56). After 15 min., two new signals in the acetyl methyl region (δ = 2.36 and 2.40) had appeared in a ratio of

approximately 4:1; these increased in area with time at the expense of the acetyl methyl peak at δ = 2.06. The aromatic region of the spectrum also changed with time, changing from a singlet in the initial spectrum to a complex multiplet centered at δ = 7.44. The spectrum of the reaction mixture after standing 24 hrs. at room temperature was found to be identical with that of an approximately 4:1 mixture of o- and p-hydroxyacetanilides treated with excess trifluoroacetic anhydride in carbon tetrachloride solution. Measurements on the relative areas of the peaks in the acetyl methyl region of the n.m.r. spectra indicated that this reaction has a half life of approximately 80 min. (at the probe temperature of approximately 37°).

The Preparation of O-Dichloroacetyl-N-acetyl-N-phenylhydroxylamine

N-Acetyl-N-phenylhydroxylamine, 3.02 g. (0.020 mole), was dissolved in 25 ml. of dry carbon tetrachloride. Dichloroacetyl chloride, 2.95 g. (0.020 mole), dissolved in 10 ml. of dry carbon tetrachloride was then added dropwise to the magnetically stirred solution, which was cooled in a salt-ice slurry. During the addition, the N-acetyl-N-phenylhydroxylamine began to crystallize from the cold solution, however this material redissolved as the reaction progressed. The odor of hydrogen chloride could be detected during and after the addition of the dichloroacetyl chloride. After completion of addition, the reaction mixture was stirred for an additional 20 min. at 0°. The solvent and dissolved hydrogen chloride were then removed by bulb to bulb distillation at room temperature under 0.05 mm. vacuum, yielding a light amber,

oily residue in the reaction flask. The n.m.r. spectrum of this oil dissolved in carbon tetrachloride indicated that it was pure O-dichloroacetyl-N-acetyl-N-phenylhydroxylamine, uncontaminated by other materials. The n.m.r. spectrum of this material exhibited the following absorptions and relative areas: singlet, δ = 1.96 (3), singlet, δ = 6.20 (1), and a singlet, δ = 7.40 (5) (all relative to tetramethylsilane as an external standard). Repeated attempts to crystallize this oil neat or from various solvents (ether, carbon tetrachloride and chloroform) failed, and it appears likely that it is a liquid at freezer temperatures.

O-Dichloroacetyl-N-acetyl-N-phenylhydroxylamine was also prepared under the same conditions, using dichloroacetic anhydride as the acylating reagent. The resulting stoichiometric amount of dichloroacetic acid produced by the reaction was found to be conveniently removed by shaking the carbon tetrachloride solution of the reaction products with an excess of anhydrous sodium carbonate, followed by vacuum filtration and evaporation of the carbon tetrachloride mother liquor, yielding an amber oil which was identical, as shown by n.m.r., with the material obtained from reaction with dichloroacetyl chloride.

Kinetics of the Rearrangement of O-Dichloroacetyl-N-acetyl-N-phenylhydroxylamine

The rearrangement of O-dichloroacetyl-N-acetyl-N-phenylhydroxylamine to o- and p-acetamidophenyldichloroacetates in dichloroacetic acid solution was found to be conveniently followed by n.m.r. techniques, which allowed, by observing the dichloromethyl proton signals, the independent observation of the disappearance of starting material (=

(δ = 6.34 relative to tetramethylsilane as an external standard) and the appearance of the ortho (δ = 6.36) and para (δ = 6.42) isomers. The relative concentrations of the isomers for a particular kinetic point were measured by determining the individual peak areas with a planimeter, and reducing these areas to percentages based on the total area of all three peaks. The sum of the three areas was found to agree well with the total area of the acetyl methyl region, giving the expected 1:3 ratio. The ortho to para ratio was found to remain constant (within the experimental error of the method) throughout the kinetic run with an average value of o/p = 3.02 ± 0.16. In this kinetic study, an approximately 20 per cent w/w solution of O-dichloroacetyl-N-acetyl-N-phenylhydroxylamine in dichloroacetic acid was weighed out into an n.m.r. tube, which was then stoppered and sealed with tape. As rapidly as possible, an initial kinetic point was obtained and then the sample was immersed in a constant temperature bath at $40.0 \pm 0.1^{\circ}$. The n.m.r. sample was then withdrawn at various time intervals and a double scan (sweep width 250, sweep time 500 sec.) was made of the N-H, aromatic, dichloroacetyl and acetyl regions, so that a complete record of appearance and disappearance of all signals was obtained. Per cent composition was obtained from peak areas measured with a planimeter. All changes in the spectra were completely in accord with the formation of the ortho and para isomers as the sole products observable by n.m.r. First-order plots of the per cent reaction for the disappearance of starting material, the appearance of the ortho isomer and the appearance of the para isomer yielded identical rate constants (k_{app} = 0.0052 min^{-1}., $t_{\frac{1}{2}}$ = 130 min.). However, during the course of rearrangement the reaction mixture acquired a dark color. It is

speculated that this coloration results from trace amounts of materials resulting from oxidization of the starting material, from the oxidization of the ortho and para isomers or from the oxidization of intermediates formed during the reaction.

The same n.m.r. technique was used to follow the rearrangement at $30.0 \pm 0.1^{\circ}$ using methoxyacetic acid as the catalyst. However in this solvent, the chemical shifts of the ortho and para isomers were not sufficiently different to allow their separate observation, although the combined signal (centered at $\delta = 6.56$ relative to tetramethylsilane as an external standard) was sufficiently different from that of the starting material ($\delta = 6.46$) to allow observation of the conversion of reactant to products. A small amount of dichloroacetic acid ($\delta = 6.20$) was found to be present in the initial scan of the reaction mixture, apparently resulting from hydrolysis of the starting material by a trace of moisture. The concentration of this impurity did not change over the course of the rearrangement. No new peaks corresponding to the formation of methoxyacetic esters were observed. The rearrangement catalyzed by methoxyacetic acid under these conditions has a half-life of approximately 80 hrs.

Treatment of O-dichloroacetyl-N-acetyl-N-phenylhydroxylamine dissolved in carbon tetrachloride with concentrated sulfuric acid resulted in a vigorous reaction and extensive decomposition to a blue, tarry material. The n.m.r. spectrum of this material indicated extensive decomposition, and no evidence for the formation of rearrangement products was found.

The Thermal Rearrangement of O-Dichloroacetyl-N-acetyl-N-phenylhydroxylamine

Vacuum distillation of O-dichloroacetyl-N-acetyl-N-phenylhydroxylamine, 2.18 g. (0.0083 mole), was attempted under a vacuum of 0.05 mm. At a pot temperature of 90-100°, the pot material darkened and appeared to undergo a change from liquid to semi-solid material. Continued heating up to 185° resulted in the vaporization of the pot material and its deposition in the cooler regions of the modified Claisen head of the distillation apparatus as a tan to white crystalline material. Under these conditions, there was also collected in the receiver two drops of an unidentified yellow oil which darkened on standing. The solid material in the Claisen head was collected by scraping and washing the apparatus with acetone, yielding, after evaporation of the acetone and vacuum drying, 1.50 g. of light tan solid, m.p. 112-116°. Recrystallization of approximately 0.20 g. of this material from boiling ether yielded glistening white needles, m.p. 120-121.5°. Hydrolysis of approximately 0.20 g. of the crude material with a neutral, aqueous-acetone solution, resulted in a strongly acidic solution, which after evaporation of the acetone, yielded light yellow crystals, m.p. 193.5-194.5°. This material was found to be identical with authentic o-hydroxyacetanilide by mixed melting point, which exhibited no depression, and by comparison of their infrared spectra, which were superimposable.

Dichloroacetic Acid-$^{18}O_2$

Dichloroacetonitrile, 28.151 g. (0.255 mole), purchased from K & K Laboratories, Inc., was placed in a 100 ml., 3-necked flask fitted

with an inlet for dry hydrogen chloride gas and a silica gel drying tube exit. Deuterium oxide, 15.3 ml. (0.765 mole), enriched in isotopic oxygen-18 content (1.51 atom per cent oxygen-18 content, purchased from YEDA Research and Development Co., Ltd.) was added to the flask and the resulting two-phase system was cooled in an ice-water bath. Dry hydrogen chloride was then slowly introduced while the two-phase mixture was stirred vigorously. After 45 min., the nitrile phase dissolved in the deuterium oxide phase and solution was accompanied by the evolution of a considerable amount of heat, which brought the aqueous phase briefly to its boiling point. At this time, ammonium chloride was observed to form as a white precipitate. After the reaction mixture had cooled, more hydrogen chloride was passed into the reaction flask for an additional 15 min. The reaction mixture was then stoppered and allowed to stand at room temperature for two hrs. Then the reaction mixture was extracted with two 50 ml. portions and one 25 ml. portion of ether. Filtration of the ether extracts yielded 8.94 g. of ammonium chloride. The ether filtrate was then evaporated under aspirator vacuum to a volume of 40 ml., filtered again to remove additional precipitated ammonium chloride, and then transfered to a 50 ml., pear-shaped flask for vacuum distillation. Vacuum distillation yielded as the first fraction a two-phase mixture composed of 5.6 ml. of water and 3.6 ml. of ether at 25°/0.05 mm. The second fraction, obtained at 46-55°/0.05 mm., was shown by n.m.r. to be identical with anhydrous dichloroacetic acid, yield 22.20 g. (65.5 per cent of theory). There remained in the distillation pot on cooling, a tan crystalline mass which was primarily dichloroacetamide, which began to sublime into the comdenser at a pot

temperature of 105°/0.05 mm.

Analysis of the mass spectrum of this material gave a ratio of peak intensities for peaks at mass 44 and 46 of 46.3 : 2.2 indicating the presence of 4.55 per cent oxygen-18 (expected 3.02 per cent). The peaks at 44 and 46 result from fragmentation of dichloroacetic acid to carbon dioxide and methylene chloride. The pattern of the peaks at masses 84, 86 and 88 present in the ratio of 9 : 6.38 : 1.38 agree well with the expected ratio[66] of 9 : 6 : 1 (as a result of the chlorine-35 and chlorine-37 isotopes) for methylene chloride.

Dichloroacetyl Chloride-^{18}O

Dichloroacetic acid-$^{18}O_2$, 21.15 g. (0.164 mole), was added dropwise to a 50 ml., pear-shaped flask containing freshly distilled phosphorus trichloride, 8.0 ml. (0.090 mole). The resulting solution was then attached to a modified Claisen distillation apparatus and carefully heated to a pot temperature of 75° and held at this temperature for two hrs. while the phosphorus trichloride refluxed. During this time, copious amounts of hydrogen chloride gas, identified by its odor, were given off. At the end of the two hr. period, refluxing had almost ceased. Then the pot temperature was increased slowly, and three distillation fractions were taken. The first fraction came over at a distillation temperature of 25-40°, yielding approximately 1-2 ml. of phosphorus trichloride. The second fraction came over at 41-91°, and appeared to be a mixture of phosphorus trichloride and dichloroacetyl chloride in a yield of 5 ml. The third fraction, which distilled between 91-94°, was found to be identical with authentic dichloroacetyl chloride by comparison with the

n.m.r. spectrum of an authentic sample (singlet at δ = 6.20 relative to tetramethylsilane as an external standard) in a yield of 8.08 g. (33 per cent of the theoretical amount). This material was found to be free of phosphorus trichloride by treating the n.m.r. sample (neat) with three drops of anhydrous methanol. This resulted in the exclusive formation, as measured by n.m.r., of methyl dichloroacetate. This analytical method has been found to be a sensitive method for the detection of phosphorus trichloride, since the reaction of methanol with phosphorus trichloride is comparable in rate with its reaction with dichloroacetyl chloride, and results in a distinctive splitting pattern in the n.m.r. spectrum for the phosphite ester formed, due to the splitting of the methyl proton signal by phosphorus.

O-Dichloroacetyl-^{18}O-N-acetyl-N-phenylhydroxylamine

Isotope oxygen-18 enriched dichloroacetyl chloride, 4.000 g. (0.0271 mole), was reacted with N-acetyl-N-phenylhydroxylamine 4.080 g. (0.0271 mole), in carbon tetrachloride solution to form O-dichloroacetyl-^{18}O-N-acetyl-N-phenylhydroxylamine as described earlier.

After removal, *in vacuo*, of the carbon tetrachloride solvent and the hydrogen chloride produced in the reaction, there was observed a trace of insoluble brown solid adhering to the walls of the reaction flask. The liquid reaction product was separated from the solid impurity by decanting to another reaction flask. An n.m.r. spectrum of the liquid reaction product in carbon tetrachloride, indicated that the liquid product is pure O-dichloroacetyl-N-acetyl-N-phenylhydroxylamine uncontaminated by rearrangement products (Fig. 2).

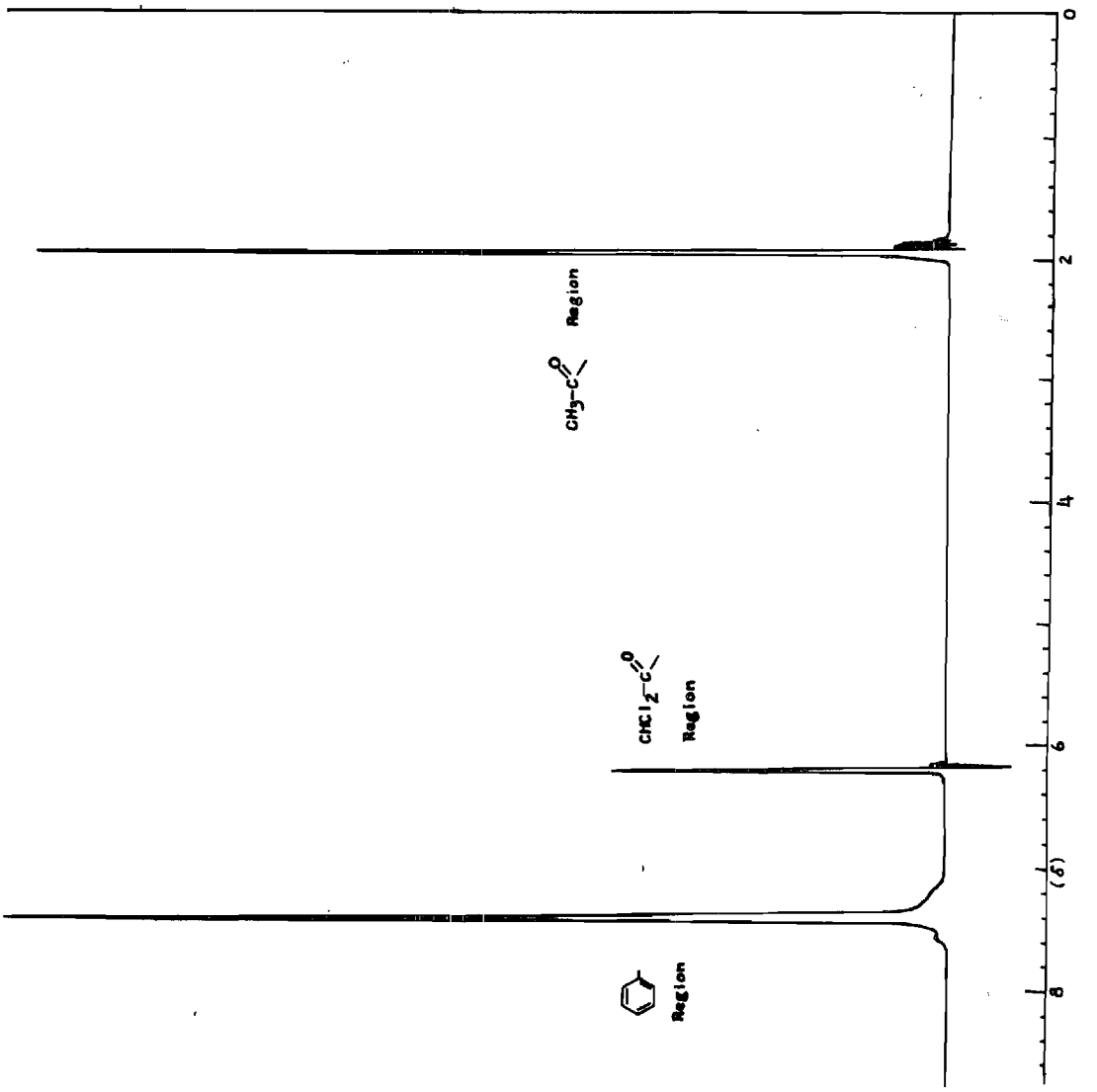

Figure 2. The N.M.R. Spectrum of O-Dichloroacetyl-N-acetyl-N-phenylhydroxylamine in Carbon Tetrachloride Solvent.

The Rearrangement of O-Dichloroacetyl-^{18}O-N-acetyl-N-phenylhydroxylamine

O-Dichloroacetyl-^{18}O-N-acetyl-N-phenylhydroxylamine, 6.3250 g. (0.0241 mole), was dissolved in 16 ml. of redistilled dichloroacetic acid (n.m.r. showed the neat acid to contain a trace impurity, which, on the basis of chemical shifts, appears to be chloroacetic acid). The resulting reaction mixture was stored in the dark under a nitrogen atmosphere at room temperature. The progress of the reaction was monitored by n.m.r., which showed the reaction to be essentially 90 per cent complete after 65 hrs. (Fig. 3). After approximately 120 hrs., the reaction mixture was poured onto ice with rapid stirring. The stirred mixture of ice, water, and insoluble reaction products was then carefully neutralized with anhydrous sodium carbonate to pH 8. The waxy, insoluble reaction products were isolated by vacuum filtration and washed with 100 ml. water. After drying for 2 hrs. under 0.05 mm. vacuum, the material weighed 7.021 g. Attempted recrystallization of this material from boiling carbon tetrachloride failed as cooling to room temperature yielded a reddish oil as a separate phase. The carbon tetrachloride solution was evaporated under 0.05 mm. vacuum to a solid residue which was partially dissolved in 100 ml. of ether. The ether insoluble material was collected on a fluted filter, and after drying, yielded 0.2645 g. of a tan solid, m.p. 166-170°. Sublimation of this material at 120-130°/0.05 mm., after recrystallization from acetone, yielded a glistening white sublimate, m.p. 197.0-197.6°. This material was found to be identical with authentic o-hydroxyacetanilide by mixed melting point, which was undepressed, and by comparison of infrared spectra, which were

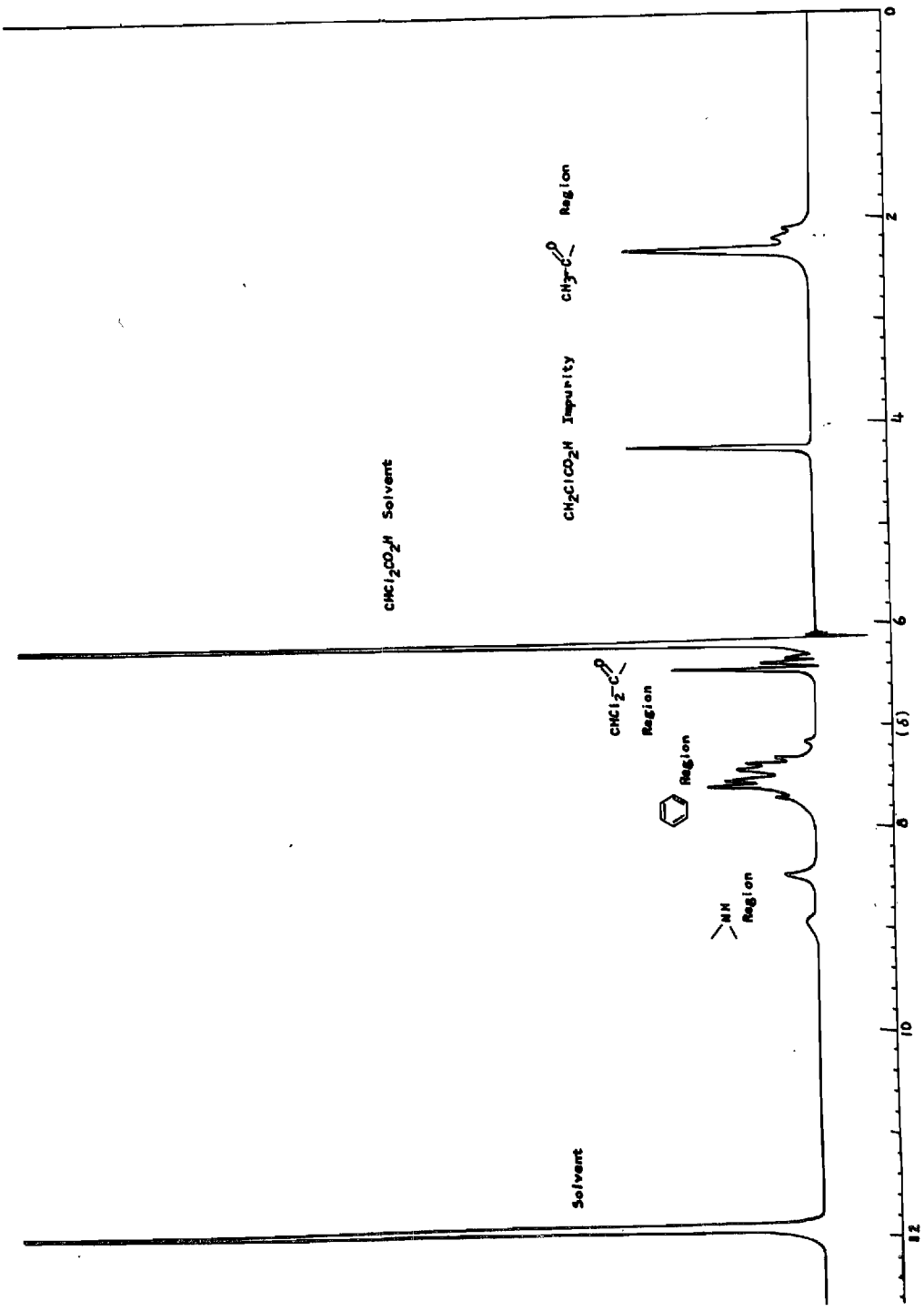

Figure 3. The N.M.R. Spectrum of the Products from the Rearrangement of O-Dichloroacetyl-^{18}O-N-acetyl-N-phenylhydroxylamine in Dichloroacetic Acid Solvent.

superimposable. Evaportion of the acetone mother liquor yielded a tan solid which sublimed at 100-120°/0.05 mm., yielding a light tan solid, m.p. 158.5-167.5°.

The ether soluble material, on cooling in the freezer, yielded, after vacuum drying, 0.5110 g. of a tacky, light tan solid, m.p. 123-127°. This material was redissolved in 50 ml. hot ether, filtered through fluted filter paper, and cooled in the freezer. Light green, almost white needles were obtained from the cooled ether solution, m.p. 134.5-135.5°. Evaporation of the ether mother liquor, followed by cooling, yielded more light green material, m.p. 135.7-137.5°, which was combined with the first fraction. An additional 0.4490 g. of this material, in a crude form, was obtained from the original mother liquor. Hydrolysis of the combined, recrystallized material in aqueous acetone solution, yielded, on evaporation of the aqueous-acetone, a tan solid which sublimed at 120°/0.05 mm., to yield an off white solid, m.p. 160-167°. This material was combined with the material melting at 158.5-167.5° from above. Resublimation of the combined material at 120-130°/0.05 mm. yielded a first fraction as a light yellow solid, m.p. 153-164°, which, after washing with a few drops of acetone gave a white material, m.p. 167-178°. A second sublimation fraction was obtained on continued sublimation, m.p. 158-168°. This material, on washing with acetone, yielded a white solid, m.p. 167-169°, which was found to be identical with authentic p-hydroxyacetanilide by mixed melting point, m.m.p. 167-170°, and by comparison of infrared spectra, which were superimposable. The mass spectrum of a sublimed sample of this material gave an M+2 peak (mass 153) intensity which was 2.38 per cent of the intensity of its parent

peak (mass 151), while an isotopically normal sample gave an M+2 peak intensity which was 1.32 per cent of the intensity of its parent peak. This corresponds to an oxygen-18 enrichment of 1.05 percent. Similarly, comparison of relative peak intensities at m/e = 109 and 111 (the fragment resulting from loss of ketene) gave an oxygen-18 enrichment of per cent, in fair agreement with the value derived from the parent peak intensities.

Combination of the various residues obtained from the evaporation in vacuo of mother liquors followed by hydrolysis in aqueous acetone, yielded, after evaporation of the acetone, 1.304 g. of a brown, solid material. Recrystallization from boiling ether yielded a light tan, crystalline material which sublimed at 130°/0.05 mm., yielding a glistening white, microcrystalline material, m.p. 202-203°, which was found to be identical with authentic o-hydroxyacetanilide by mixed melting point, which was undepressed, and by comparison of infrared spectra, which were superimposable. The mass spectrum of a sublimed sample of this material gave an M+2 peak (mass 153) intensity which was 2.24 per cent of the intensity of its parent peak (mass 151), while an isotopically normal sample gave an M+2 peak intensity which was 1.27 per cent of the intensity of its parent peak. This corresponds to an oxygen-18 enrichment of 0.96 per cent.

N-Acetyl-O-phenylhydroxylamine

Diphenyliodonium bisulfate, 7.56 g. (0.02 mole), was placed in the reaction bulb of the degassing apparatus, bulb A (Fig. 1), and dissolved in 100 ml. of aqueous 0.40 N sodium hydroxide.

N-Acetylhydroxylamine, 1.50 g. (0.02 mole), was placed in the side-arm bulb B (Fig. 1) of the apparatus. The aqueous diphenyliodonium ion solution was then degassed by the freezing-thawing technique through three freezing cycles under 0.05 mm. vacuum before mixing the solution with the N-acetylhydroxylamine. After the reaction mixture had stood at room temperature for two days under vacuum, it was then extracted with three 30 ml. portions of stock ether. The combined ether extract was washed with 30 ml. of 0.40 N sodium hydroxide, and evaporated under vacuum. The Dry Ice trap yielded approximately 1.25 ml. of iodobenzene. The brown solid evaporation residue, yield 0.30 g., which remained from ether evaporation was not identified.

Treatment of the aqueous phase (pH 8) of the reaction mixture with excess sodium bromide precipitated unreacted diphenyliodonium ion as its insoluble bromide salt, yield 3.63 g. (0.010 mole), m.p. 204-206° (reported,[63] m.p. 208-209°). When the aqueous phase was neutralized to pH 6, there formed a colorless crystalline solid, dec. 157-158°, in a yield of 0.36 g. Extraction of the aqueous phase with stock ether, followed by evaporation, yielded 0.44 g. more of this material, dec. 156-158°. The total yield of this material, assigned the structure N-acetyl-O-phenylhydroxylamine, was 0.80 g. (54.7 per cent of the theoretical amount after correction for unreacted diphenyliodonium ion). Sublimation at 80°/0.1 mm. gave glistening white needles, m.p. 157.6-158.4° (reported,[77] 157-158.5°). The infrared spectrum of this material

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(77) C. L. Bumgardner and R. L. Lilly, Chem. Ind., (London), 559 (1962).

exhibited characteristic absorptions at $\bar{\nu}$ = 3125, 1668, and 1600 cm^{-1}. The n.m.r. spectrum of this material in deuterochloroform exhibited the following absorptions (relative to tetramethylsilane as an external standard) and relative areas: a singlet at δ = 2.08 (3) and a complex multiplet at δ = 7.15 (5).

O-Phenylhydroxylammonium Chloride

N-Acetyl-O-phenylhydroxylamine, 0.59 g. (0.0039 mole), was dissolved in 25 ml. of absolute ethanol. This solution was acidified with a stream of dry hydrogen chloride and then refluxed for 25 min. Evaporation of the solution to a volume of 3-5 ml. followed by dilution with 120 ml. of ether precipitated almost white platelets of O-phenylhydroxylammonium chloride, yield after vacuum drying, 0.45 g., m.p. 130-133° (reported,[78] m.p. 134° dec.). This material, 0.10 g. (0.0007 mole), was then dissolved in 5 ml. of water and neutralized with 1.4 ml. of 0.40 N sodium hydroxide. The solution immediately turned a milky light yellow. Addition of 0.07 ml. of acetic anhydride to this mixture precipitated a white crystalline material, dec. 156-158°, which was shown to be identical with the starting material, O-phenyl-N-acetylhydroxylamine, by mixed melting point, which was undepressed.

3,5-Dibromo-1-anilino-1-methylcyclohexadien-4-one

This material was prepared by the method of Fries and Oehmke[79] by the reaction of aniline with 1,3,5-tribromo-1-methylcyclohexadien-4-one[79] in ethanol.

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(78) J. S. Nicholson and D. A. Peak, Chem. Ind. (London), 1244 (1962).

(79) K. Fries and G. Oehmke, Ann., 462, 1 (1928).

Attempted Acylation of 3,5-Dibromo-1-anilino-1-methyl-cyclohexadien-4-one with Acetic Anhydride

Treatment of the quinamine with excess acetic anhydride for 15 min. at room temperature followed by heating to 60° for 30 min. and then hydrolysis of the excess acetic anhydride with approximately 1 N sodium hydroxide precipitated a light purple solid, dec. 175-182°. This material was found to be identical with an authentic sample of 4-acetamido-2',6'-dibromo-4'-methyldiphenylether by mixed melting point, which was undepressed, and by comparison of infrared spectra, which were superimposable. The authentic material was prepared by rearrangement of the quinamine in methanolic hydrogen chloride,[79] followed by acylation of the resulting 4-amino-2',6'-dibromo-4'-methyldiphenylether with acetic anhydride, m.p. 183-186° (reported,[79] 186°).

Attempted acylation under milder conditions (acetic anhydride in triethylamine or acetic anhydride and sodium carbonate at room temperature for several days) failed to yield anything but unreacted starting material.

Phenylsulfenyl Chloride

Phenylsulfenyl chloride was prepared by the method of Lecher, et al.,[80] by the chlorinolysis of diphenyldisulfide in carbon tetrachloride with dry chlorine gas.

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(80) H. Lecher, F. Holschneider, K. Koberle, W. Speer and P. Stocklin, Chem. Ber., 58, 409 (1925).

N,S-Diphenylthiohydroxylamine

N,S-Diphenylthiohydroxylamine was prepared by the reaction of phenylsulfenyl chloride with aniline (freshly distilled) in dry ether solution, also after the method of Lecher, et al.[80]

Reaction of N,S-Diphenylthiohydroxylamine with Acid

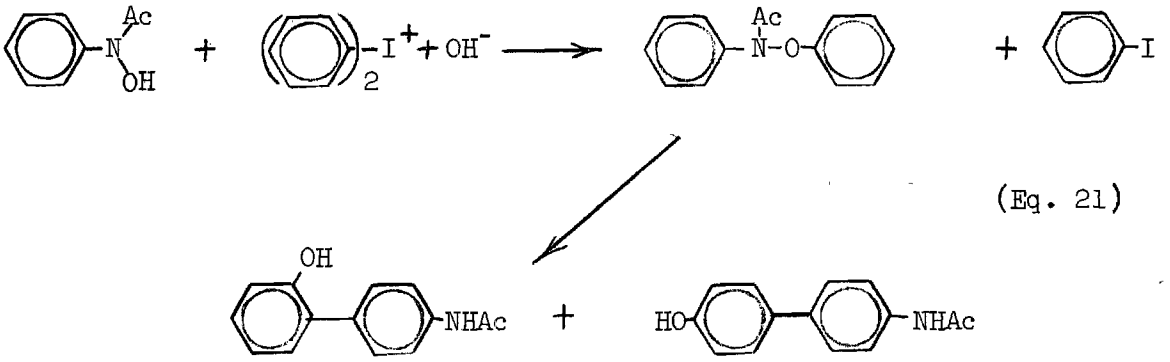
Treatment of N,S-diphenylthiohydroxylamine with dilute hydrogen chloride, sulfuric acid or perchloric acid in ethanol was found to yield aniline and diphenyldisulfide. No evidence could be found for benzidine-like rearrangement products among the products of reaction.

CHAPTER V

DISCUSSION OF RESULTS

The Reaction of N-Acetyl-N-phenylhydroxylamine with Diphenyliodonium Ion

The products derived from the reaction of diphenyliodonium hydroxide with N-acetyl-N-phenylhydroxylamine are most easily interpreted as arising from the intermediacy of O,N-diphenyl-N-acetyl-N-phenylhydroxylamine, which spontaneously rearranges to the observed products, 2'- and 4'-hydroxy-4-acetamidobiphenyl, as shown in Eq. 21.



(Eq. 21)

However, at least one other pathway to the observed products could be visualized.[81] This pathway is shown in Eqs.22-24.

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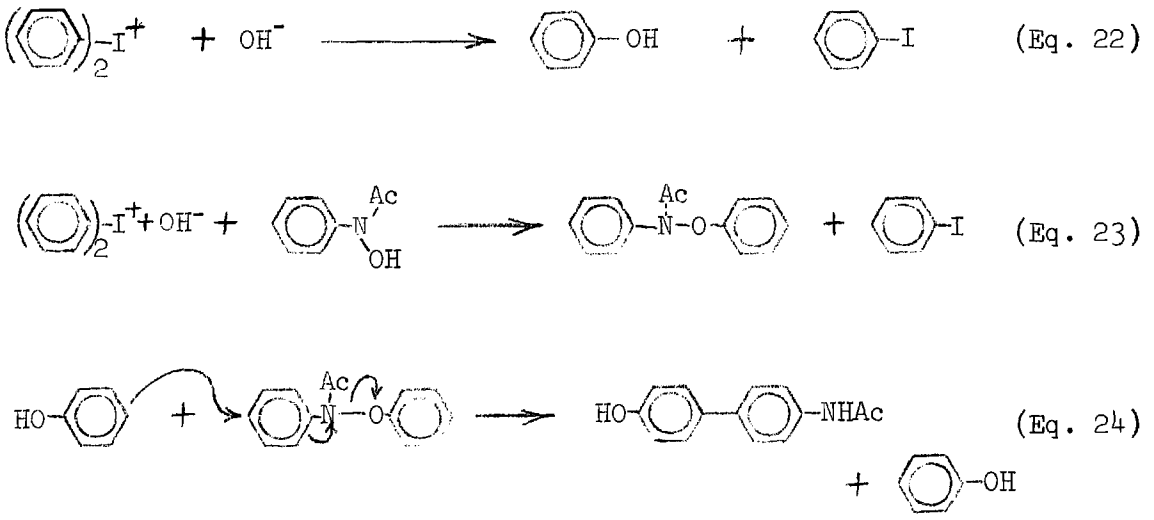
(81) Dr. Jack Hine is thanked for the suggestion of this pathway.



(Eq. 22)

(Eq. 23)

(Eq. 24)

Although this pathway was thought to be unlikely, the known, acid-catalyzed intermolecular conversion of N-phenylhydroxylamine to 4'-hydroxy-4-aminobiphenyl,[52] in the presence of phenol could be construed as precedent.

The finding that 4'-hydroxy-4-acetamidobiphenyl isolated from the reaction of N-acetyl-N-phenylhydroxylamine with diphenyliodonium hydroxide in oxygen-18 enriched water contained no more than the normal abundance of oxygen-18, clearly eliminates the above pathway and any other pathway which would have the 4'-hydroxy oxygen originate from a solvent molecule. This result provides strong evidence for the intermediacy of O,N-diphenyl-N-acetyl-N-phenylhydroxylamine, however, it does not provide any information about the inter- versus intramolecularity of its subsequent rearrangement.

The lack of any excess oxygen-18 in the 4'-hydroxy-4-acetamidobiphenyl isolated from the reaction of N-acetyl-N-phenylhydroxylamine

with diphenyliodonium ion in the presence of one equivalent of oxygen-18 labeled phenol provides good evidence for an intramolecular pathway. This experiment appears to eliminate an intermolecular pathway involving radicals, in addition to the polar-chain mechanism (Eqs. 22-24), as incorporation of enriched phenol would be expected to occur. The occurrance of an ionic intermolecular pathway involving a phenoxonium ion and an acetanilide-anion is not ruled out by this labeling experiment, however, such a pathway is considered highly unlikely, as under the mild conditions of the reaction, the acetanilide-anion would immediately extract a proton from the solvent to yield acetanilide, and the phenoxonium ion would immediately react with water to yield hydroquinone.

That the rearrangement of the intermediate O,N-diphenyl-N-acetyl-N-phenylhydroxylamine is spontaneous, and not an artifact of the isolation procedure is attested to by the close similarity of the infrared spectrum[71] of the crude reaction products with that of the purified 4'-hydroxy isomer.

Rearrangement of N-Acetylhydrazobenzene

The isolation of benzidine from the rearrangement of N-acetylhydrazobenzene under dilute acid conditions suggests that rearrangement takes place only after hydrolysis (or alcoholysis) of the N-acetyl derivative to hydrazobenzene has taken place, although hydrolysis after rearrangement could not be ruled out. The findings of Vecera, et al.,[82] support a pathway which has hydrolysis of the N-acetyl group as its

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(82) M. Vecera, J. Petranek and J. Gasparic, Coll. Czech. Chem. Comm., 22, 1063 (1957).

first step, since they were unable to find evidence for products other than benzidine and diphenyline from the treatment of N-acetylhydrazobenzene with dilute mineral acid. Furthermore, the ultraviolet spectrum of the products derived from treatment of N-acetylhydrazobenzene with 1 N perchloric acid (30 per cent methanol-water) is identical with the spectrum of the products obtained from the rearrangement of hydrazobenzene under identical conditions.

The rearrangement of N-acetylhydrazobenzene under conditions of concentrated mineral acid presents quite a different situation. On treatment with concentrated mineral acid, N-acetylhydrazobenzene affords N-acetylbenzidine as the only product. This finding is in good agreement with the previous findings of Pongratz and Scholtis.[83] The isolation of N-acetylbenzidine in yields as high as 91.5 per cent, and the observation of an isosbestic point in the ultraviolet spectrum during the course of the rearrangement demonstrate that N-acetylbenzidine is the sole product of rearrangement.

The change in the character of the reaction of N-acetylhydrazobenzene under acidic conditions on going from dilute to concentrated acid media is undoubtedly a direct result of the decrease in solvent activity which occurs as the acidity increases. The hydrolysis studies of Krieble and Holst[84] clearly demonstrate that the solvent activity is important to amide solvolysis. They found that the rates of solvolysis

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(83) A. Pongratz and K. Scholtis, Chem. Ber., 75, 138 (1942).
(84) V. K. Krieble and K. A. Holst, J. Am. Chem. Soc., 60, 2976 (1938).

of formamide, acetamide and propionamide all go through maxima as the acid concentration increases. Thus, since rearrangement is expected to be a function of the Hammett acidity only,[13,47,49] the situation which obtains in the case of N-acetylhydrazobenzene depends upon the relative rates of solvolysis *versus* rearrangement.

The vigorous conditions which are necessary for the rearrangement of N-acetylhydrazobenzene to N-acetylbenzidine demanded that the intramolecularity of the reaction be established to insure that the reaction is truly a manifestation of the benzidine rearrangement.

The mixed rearrangement of 2,3,4,5,6,2',3',4',5',6'- decadeutero-N-acetylhydrazobenzene and isotopically normal N-acetylhydrazobenzene in 6.01 *F* perchloric acid provides a test for the intramolecularity of the rearrangement, by examining the mass spectrum of the reaction products. If the rearrangement is intramolecular, then the mass spectrum of the products should exhibit a parent peak at mass 226 for the normal material and a parent peak at mass 234 for the octadeutero material. The peak at mass 230 is a direct measure of the intermolecularity of the reaction, since it corresponds to the parent peak of the cross-product. The mass spectral data for the mixed reaction and for authentic samples of isotopically normal and ring deuterated rearrangement products are summarized in Table 2. These data clearly demonstrate that not more than 0.2 per cent of the rearrangement occurs *via* an intermolecular pathway. Exchange of the ring deuterium atoms under the conditions of the rearrangement was not found to be a significant reaction, as the authentic deuterium labeled material obtained from rearrangement of the ring deuterated N-acetylhydrazobenzene had a ring deuterium content of at

least 98.8 per cent deuterium as measured by the peak of mass 233 relative to its parent peak of mass 234.

Table 2. The Mass Spectra of the Products from the Rearrangements of 2,3,4,5,6,2',3',4',5',6'-Decadeutero-N-acetylhydrazobenzene and N-Acetylhydrazobenzene in 6.01 F $HClO_4$

Material	relative peak intensities Mass 226	230	234
Isotopically Normal	248	~2	~2
Authentic Perdeutero	8	—	675
Rearrangement Mixture (42.1 per cent protio and 57.9 per cent perdeutero)	348	~0.75	498

Preliminary kinetic measurements on the acid-catalyzed conversion of N-acetylhydrazobenzene to benzidine and presumably diphenyline in 30 per cent methanol-water solution were obtained by following the ultraviolet spectral changes of neutralized aliquots at λ_m = 235 mμ for the disappearance of N-acetylhydrazobenzene and at λ_m = 280 mμ for the appearance of benzidine after the method of Carlin, Nelb and Odioso.[85] The results of these studies are tabulated in Table 3.

(85) R. B. Carlin, R. G. Nelb and R. C. Odioso, J. Am. Chem. Soc., 73, 1002 (1951).

Table 3. The Acid-Catalyzed Reaction of N-Acetylhydrazobenzene to Benzidine in 30 Per Cent Methanol-Water Solutions

T* (°C)	$[H^+]$ $HClO_4$	$NaClO_4$	k_h** (hr^{-1})	$t_{h\frac{1}{2}}$ (hr)	$\frac{k_h}{[H^+]}$	k_b** (hr^{-1})	$t_{b\frac{1}{2}}$ (hr)	$\frac{k_b}{[H^+]}$
30.0	1.080	0.000	0.040	17	0.035	0.038	18	0.035
"	0.753	0.227	0.025	28	0.033	0.025	28	0.033
"	0.540	0.520	0.020	35	0.037	0.019	37	0.035
"	0.374	0.706	0.015	46	0.040	0.016	42	0.044
60.0	1.080	0.000	0.59	1.2	0.54	0.58	1.2	0.53

* The temperature was controlled within $\pm 0.1^{\circ}$.
** The rate constant k_h is the apparent rate of disappearance of N-acetylhydrazobenzene and k_b is the apparent rate of formation of benzidine.

Comparison of the relative rates of reaction at 30.0° and at 60.0° gives an approximate energy of activation of 18.4 Kcal/mole. Inspection of the calculated, second-order rate constants in Table 3. indicates that the reaction is of second order, first order with respect to N-acetylhydrazobenzene and first order with respect to hydrogen ions. Furthermore, the data in Table 3. demonstrate that the rate of reaction of N-acetylhydrazobenzene and the rate of formation of benzidine are identical.

It was anticipated that under conditions of concentrated acid, where the predominant course of the rearrangement is the formation of N-acetylbenzidine, the rearrangement would be dependent on the Hammett acidity of the reaction media. In order to establish a dependence on

the Hammett acidity, kinetic studies were carried out in the aqueous perchloric acid-sodium perchlorate system used by Harbottle.[86] This system, in which the total perchlorate ion formality is maintained at 6.00 F, was chosen, after consideration of the literature on Hammett acidity functions, for its low water activity, which the constant perchlorate ion formality imparts to the solutions, and for the linearity of its acidity function over the range 2-6 F perchloric acid. An additional advantage of this system is that this acidity range results in apparent rearrangement rates which are conveniently studied by conventional methods at easily accessible temperatures. The Hammett acidity values (H_o) for Harbottle's system are listed in Table 4. along with rate data, and a plot of H_o versus perchloric acid formality is shown in Fig. 4.

The kinetics of the rearrangement of N-acetylhydrazobenzene to N-acetylbenzidine were measured by following the ultraviolet spectral changes in optical density at 268 mμ , where N-acetylbenzidinium ion has a strong absorption maximum. The measurements were made directly on the concentrated acid solutions. The results of these measurements are presented in Table 4, and a typical first-order plot of the kinetic data is shown in Fig. 5.

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(86) G. Harbottle, J. Am. Chem. Soc., 73, 4024 (1951).

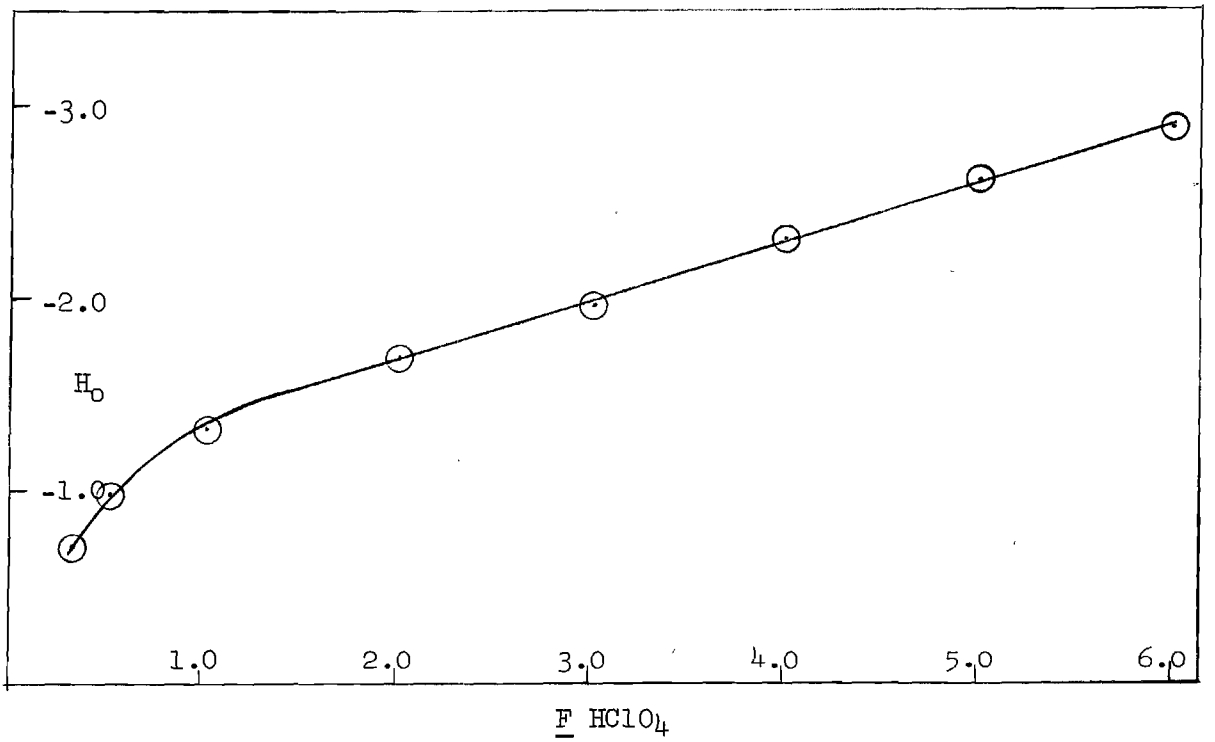

Figure 4. A Plot of the Hammett Acidity, H_o, versus Perchloric Acid Formality for Solutions of Perchloric Acid-Sodium Perchlorate 6 F in Perchlorate Ion.

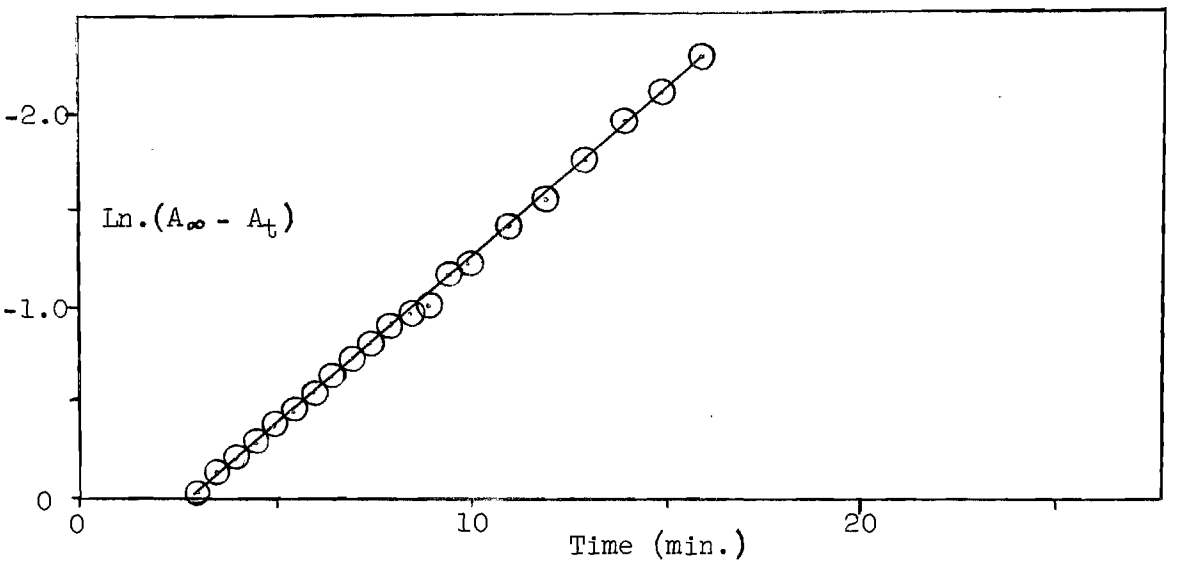

Figure 5. Ln.$(A_\infty - A_t)$ versus Time (min.) for the Rearrangement of N-Acetylhydrazobenzene in 6.01 F Perchloric Acid at 30±0.1° C.

Table 4. The Acid-Catalyzed Rearrangement of N-Acetylhydrazobenzene to N-Acetylbenzidine in Concentrated Perchloric Acid-Sodium Perchlorate

T* (°C)	$\underline{F}$ $HClO_4$	$\underline{F}$ $NaClO_4$	$-H_o$	h_o**	k_{app}*** (min^{-1})	$t_{\frac{1}{2}}$ (min)	k_{app}/h_o x10^4	$k_{app}/\underline{F}[H^+]$ x10^2
30.0	6.01	0.00	2.92	832	0.175	3.96	2.10	2.92
"	5.50	0.50	2.78	605	0.143	4.84	2.36	2.60
"	5.00	1.00	2.64	437	0.110	6.30	2.51	2.20
"	4.50	1.50	2.49	302	0.0872	7.95	2.89	1.94
"	4.00	2.00	2.40	218	0.0548	11.9	2.68	1.46
"	3.00	3.00	2.00	108	0.0321	21.6	2.97	1.07
"	2.00	4.00	1.76	53	0.0184	37.1	3.47	0.92
20.0	6.01	0.00	2.92	832	0.0467	14.8		
"	5.00	1.00	2.64	437	0.0284	24.4		

* The temperature was controlled to $\pm 0.1^o$.
** These values were obtained from the relationship $H_o = -\log h_o$.
*** The reproducibility of k_{app} was 0.005 min^{-1}.

The rate data at 30.0° and at 20.0° allow the activation energy for the rearrangement to be estimated as 23.5 Kcal/mole. A plot of H_o *versus* log k_{app} (Fig. 6) gives a linear correlation with a slope of 0.833, while a plot of log H *versus* log k_{app} (Fig. 7) gives a nonlinear correlation. The linear correlation of H_o with log k_{app} is good evidence that the rearrangement has a first-order dependence[87] on the Hammett acidity of the media. Thus, the rate data are found to fit the

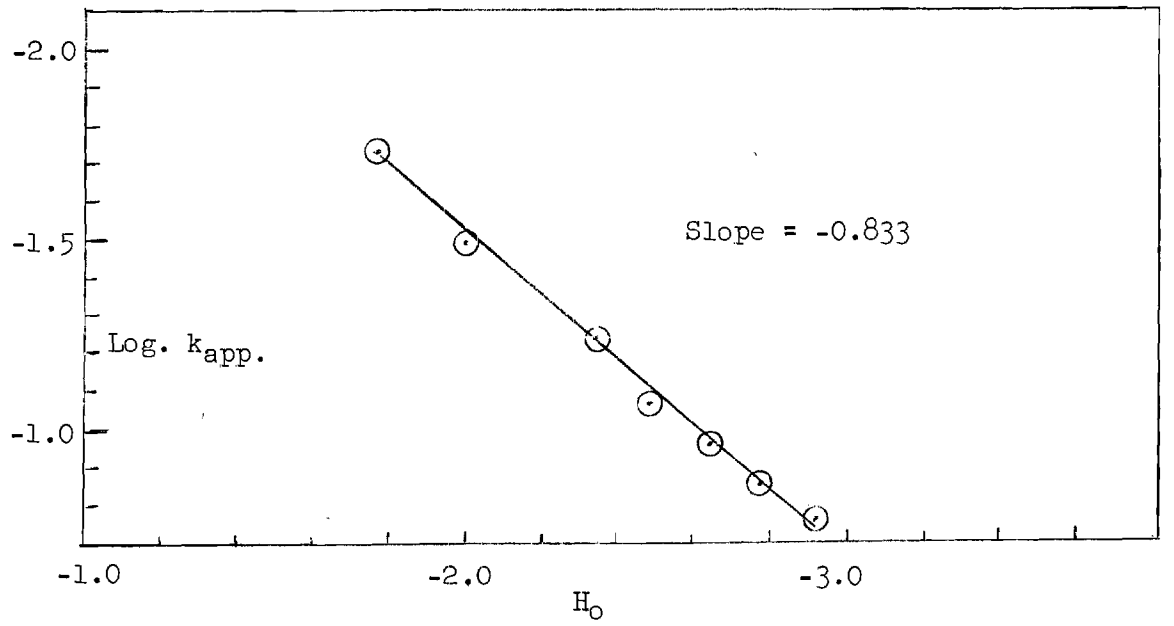

Figure 6. H_o versus Log. $k_{app.}$ for the Rearrangement of N-Acetylhydrazobenzene in Solutions of Perchloric Acid-Sodium Perchlorate 6 F in Perchlorate Ion.

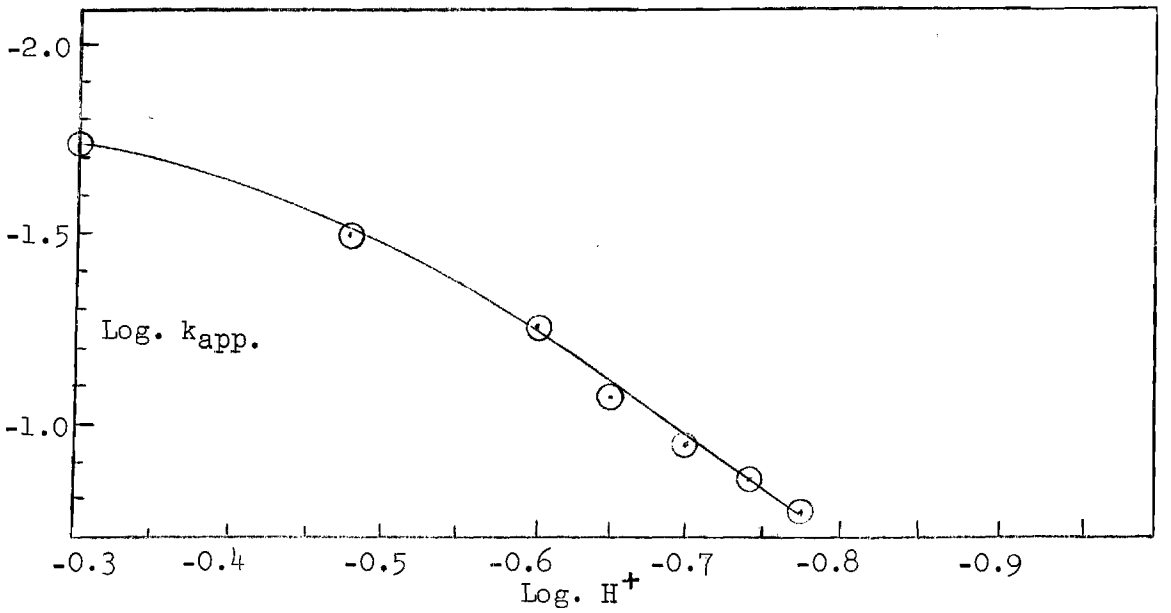

Figure 7. Log. H^+ versus Log. $k_{app.}$ for the Rearrangement of N-Acetylhydrazobenzene in Solutions of Perchloric Acid-Sodium Perchlorate 6 F in Perchlorate Ion.

empirical relationship

$$v = k_2[\text{N-acetylhydrazobenzene}]\ [h_o]^{0.833}$$

The deuterium solvent isotope effect upon the rate of rearrangement of N-acetylhydrazobenzene was measured in 6.01 F deuteroperchloric acid solution. The results of these measurements are compared with the rate of rearrangement in isotopically normal perchloric acid in Table 5.

Table 5. The Deuterium Solvent Isotope Effect on the Rate of Rearrangement of N-Acetylhydrazobenzene at 30.0°.

Conditions	$k_{app}(min^{-1})$	$t_{\frac{1}{2}}(min)$
6.01 F $HClO_4$-H_2O	0.175	3.96
6.01 F $DClO_4$-D_2O	0.149	4.65

The experimental rate constants in Table 5 give a deuterium solvent isotope effect of $k_{H_2O}/k_{D_2O} = 1.27$. This effect is considerably greater than the experimental error (0.005 min^{-1}.) involved in the method of rate determination, and undoubtedly is real.

The substrate deuterium isotope effect was determined on 2,3,4,-5,6,2',3',4',5',6'-decadeutero-N-acetylhydrazobenzene to insure the validity of the mixed rearrangement test of the intramolecularity of the rearrangement, since if the rearrangement of ring deuterated and

(87) The use of a more suitable set of indicators for the evaluation of H_o should result in a h_o dependence of unity (R. L. Hinman and J. Lang, J. Am. Chem. Soc., 86, 3796 (1964), and E. M. Arnett and G. W. Mach, ibid., 88, 1177 (1966).

isotopically normal material did not have similar rates of rearrangement, then no cross-products would result from an intermolecular pathway. In addition, the magnitude of any observed deuterium isotope effect would have other mechanistic implications which could contribute to a fuller understanding of this rearrangement. The results of these studies are given in Table 6, where they are compared with the rate of rearrangement of isotopically normal material under the same conditions.

Table 6. Substrate Deuterium Isotope Rate Effects on the Rearrangement of N-Acetylhydrazobenzene at 30.0°

Substrate	F $HClO_4$	k_{app} (min^{-1})	$t_{\frac{1}{2}}$(min)
N-acetylhydrazobenzene	6.01	0.175	3.96
2,3,4,5,6,2',3',4',5',6'-decadeutero-N-acetylhydrazobenzene	6.01	0.164	4.23

Here again, the magnitude of the rate decrease exhibited by the perdeutero material, though small (k_H/k_D = 1.07), falls outside the limits of the experimental error (0.005 min^{-1}.). To insure that this decrease in rate was not a result of experimental error, alternate runs on each material were carried out using the same stock solution of acid.

The magnitude and direction of both the solvent deuterium isotope effect and the substrate deuterium isotope effect on the rate of reaction suggests that both are secondary isotope effects.

The lack of a large equilibrium protonation isotope effect on the rate of rearrangement in deuteroperchloric acid, such as those observed

for other examples of the benzidine rearrangement,[13,20,21] could not have been predicted. However, it has been found experimentally that D_o, the Hammett acidity function of deuterosulfuric acid, is numerically the same as H_o for solutions of the same concentration,[88] and thus the deuteron-donating ability of deuterosulfuric acid is numerically the same as the proton-donating ability of isotopically normal sulfuric acid. Equilibrium isotope effects then arise from differences in the equilibrium constants for the following reactions (Eqs. 25 and 26), where B is a moderately weak base, and the difference in the equilibrium constants is a function only of the zero point energies of the species BD^+ and BH^+.

$$D_2SO_4 + B \underset{}{\overset{K_D}{\rightleftharpoons}} B\,D^+ + DSO_4^- \qquad \text{(Eq. 25)}$$

$$H_2SO_4 + B \underset{}{\overset{K_H}{\rightleftharpoons}} B\,H^+ + HSO_4^- \qquad \text{(Eq. 26)}$$

However, as the base strength of B decreases, the ratio K_D/K_H approaches unity[89] because as the difference in the ground state energies between B and BH^+ and B and BD^+ increases (i.e. as B becomes less basic), the difference between the zero point vibrational energies of BH^+ and BD^+ becomes a smaller percentage of the total ground state energy difference between B and its conjugate acid, which is measured by K_H and K_D.

The decreased rate in deuteroperchloric acid then becomes understandable as a secondary isotope effect, if it is assumed that the ratio

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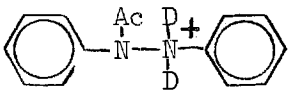
(88) E. Hogfelt and J. Bigeleisen, J. Am. Chem. Soc., 82, 15 (1960).

(89) R. P. Bell, "The Proton in Chemistry", Cornell University Press, Ithaca, New York, 1959, pp. 187.

K_D/K_H for N-acetylhydrazobenzene is close to unity, and that the rearranging species in deuteroperchloric acid is the conjugate acid of N-acetyl-N-deuterohydrazobenzene.



(Eq. 27)

Although substrate kinetic isotope effects have not been reported in other examples of the acid-catalyzed benzidine rearrangement, the finding of a small substrate isotope effect in the solvolysis of methyl-p-tolylcarbinyl chloride containing a highly deuterated p-methyl group[90] is ample precedent for a secondary isotope effect, when the isotopic substitution is not directly associated with the atoms involved in bond scission or formation. Thus, the isotope effect on the rate of rearrangement of 2,3,4,5,6,2',3',4',5',6'-decadeutero-N-acetylhydrazobenzene is probably a secondary isotope effect associated with the rate of nitrogen-nitrogen bond scission, rather than a secondary isotope effect on the formation of the carbon-carbon bond at the 4-4' positions, although this possibility cannot be completely discounted.

The Reaction of N-Acetyl-N-phenylhydroxylamine with p-Toluenesulfonyl Chloride and Methanesulfonyl Chloride

The isolation of o-acetamidophenyl-p-toluenesulfonate in 63 per cent and p- acetamidophenyl-p-toluenesulfonate in 7.1 per cent of theory

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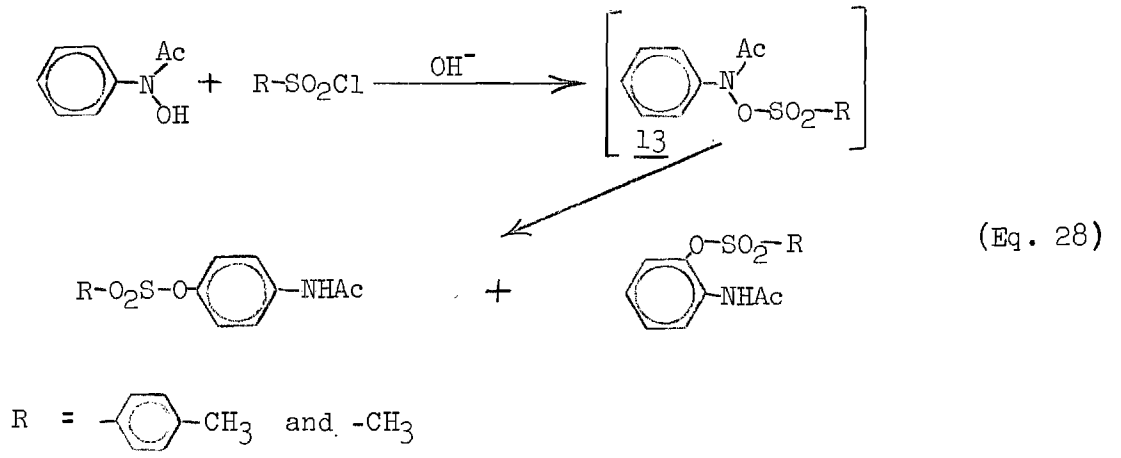
(90) E. S. Lewis and G. M. Coppinger, J. Am. Chem. Soc., 76, 4495 (1954).

under mild, non-acidic workup conditions from the treatment of N-acetyl-N-phenylhydroxylamine with p-toluenesulfonyl chloride, strongly implies that this transformation takes place via the intermediacy of N-acetyl-O-p-toluenesulfonyl-N-phenylhydroxylamine (13), which undergoes a spontaneous rearrangement to the observed products. Furthermore, the high yield of the ortho isomer in this reaction, and also in the reaction with methanesulfonyl chloride, strongly implies that the rearrangement of this intermediate is an intramolecular process.



(Eq. 28)

R = and -CH3

The Acylation of N-Acetyl-N-phenylhydroxylamine

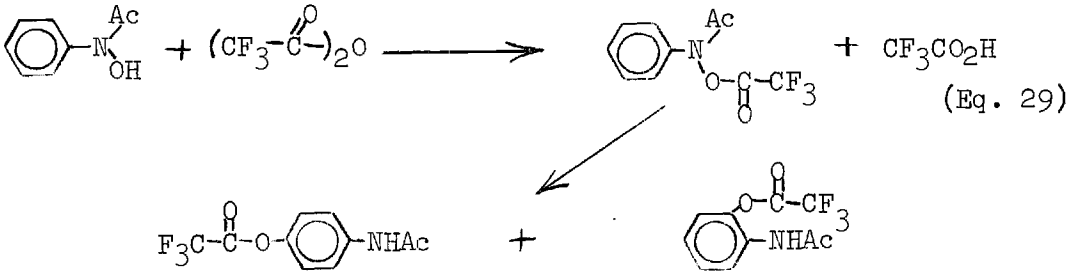
The isolation of rearranged products from the treatment of N-acetyl-N-phenylhydroxylamine with tosyl chloride and mesyl chloride and the fact that O,N-diacetyl-N-phenylhydroxylamine is a relatively stable, isolable material[75] suggested that the rearrangement of the tosyl and mesyl groups and the lack of rearrangement of the acetyl group were related to the electron-withdrawing character of the substituent, which is in turn related to the stability of the corresponding anion (e.g. the p-toluenesulfonate ion as compared to the acetate ion) rather than to

anion nucleophilicity.

A study of the reaction of N-acetyl-N-phenylhydroxylamine with a series of halogenated acetyl derivatives was undertaken, therefore, to test this hypothesis.

The Reaction of N-Acetyl-N-phenylhydroxylamine with Trifluoroacetic Anhydride

The n.m.r. traces in Fig. 8 clearly demonstrate that N-acetyl-N-phenylhydroxylamine reacts with trifluoroacetic anhydride in carbon tetrachloride to form initially O-trifluoroacetyl-N-acetyl-N-phenylhydroxylamine, which then rearranges at a moderate rate ($t_{\frac{1}{2}} \simeq 80$ min.) to a mixture of o- and p-acetamidophenyltrifluoroacetate at probe temperatures (approximately 37°). Although this rearrangement may be catalyzed by the trifluoroacetic acid produced in the reaction, other n.m.r. and infrared spectral studies on the reaction in the presence of triethylamine indicate that rearrangement still takes place in the absence of acid. Product isolations as well as the n.m.r. studies (Fig. 8) show the predominant course of the rearrangement to be the formation of the ortho isomer (approximately 80 per cent) along with some of the para isomer (approximately 20 per cent), and thus it is likely that this rearrangement is also an intramolecular process.



(Eq. 29)

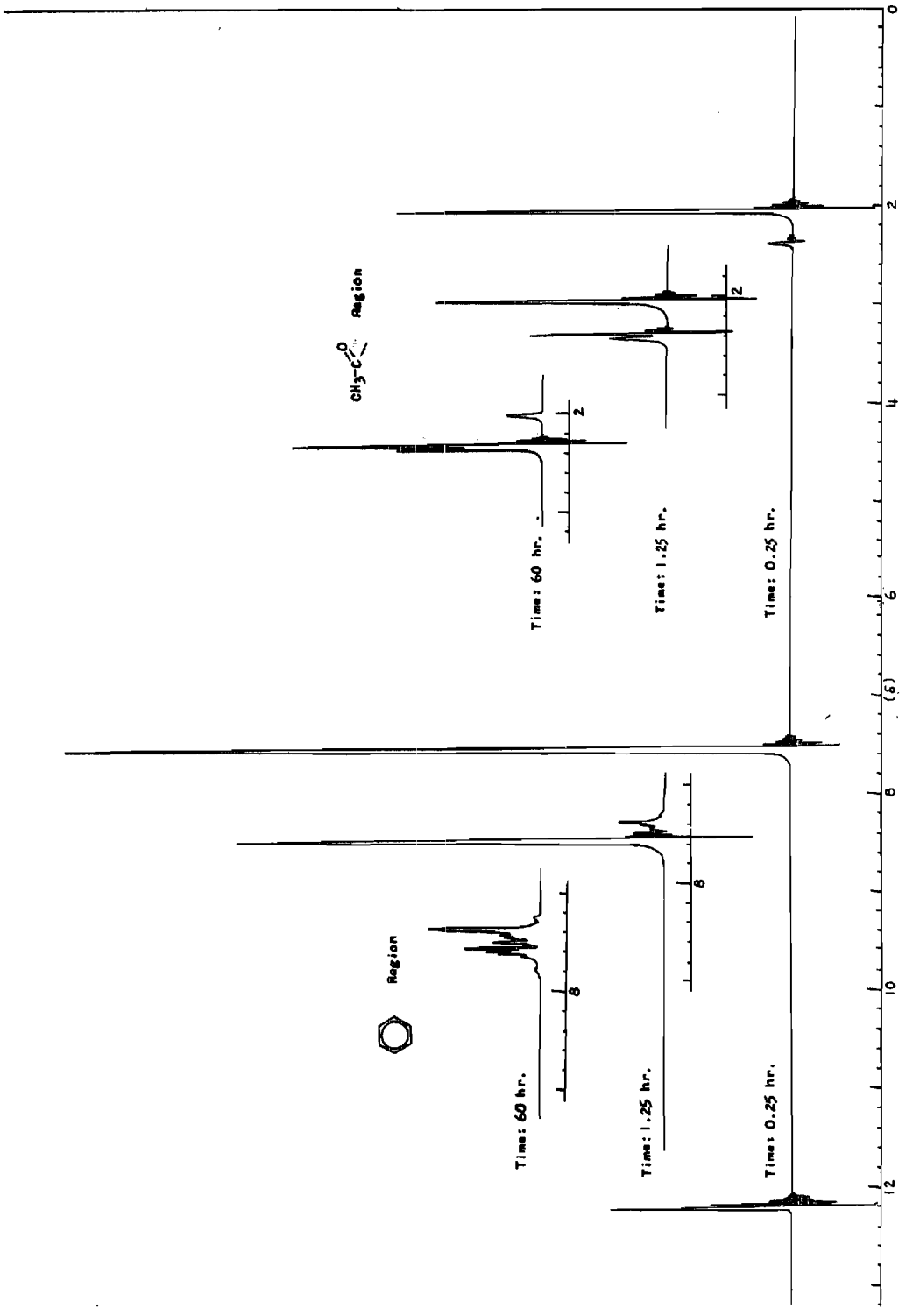
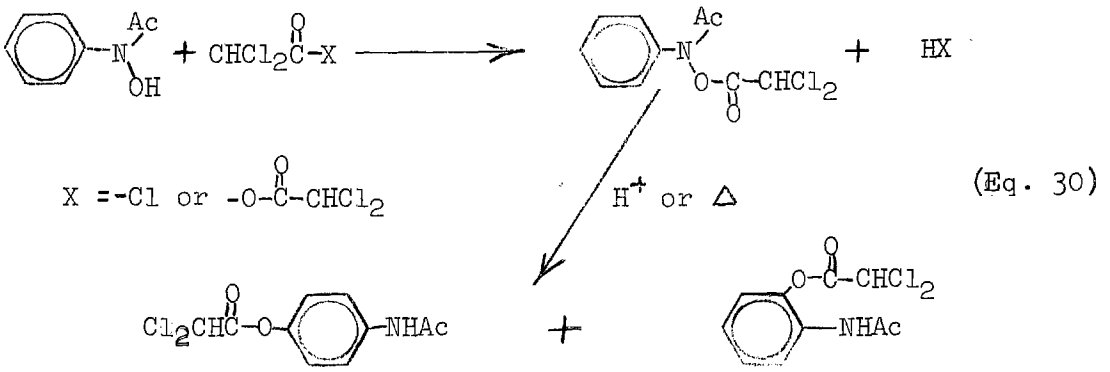


Figure 8. An N.M.R. Study of the Rearrangement of O-Trifluoroacetyl-N-acetyl-N-phenylhydroxylamine in Carbon Tetrachloride Solution.

The relatively rapid rate of rearrangement of the initial product of reaction and the ease with which it is hydrolyzed by trace amounts of moisture prevented the isolation of the unrearranged material from the reaction mixture.

The Reaction of N-Acetyl-N-phenylhydroxylamine with Dichloroacetyl Chloride and Dichloroacetic Anhydride

The reaction of N-acetyl-N-phenylhydroxylamine with dichloroacetyl chloride or with dichloroacetic anhydride (Eq. 30) proved to be a much more tractable system to study, and it was found that the unrearranged material, O-dichloroacetyl-N-acetyl-N-phenylhydroxylamine, could be isolated as a viscous liquid. The rate of rearrangement of this material at 40° in aprotic solvents (carbon tetrachloride and dimethylsuloxide) was negligible. However, it was found that heating to 90-100° under vacuum or treatment with anhydrous acids resulted in rearrangement to the ortho, along with traces of the para isomer.



(Eq. 30)

The dichloromethyl proton signal in the n.m.r. was found to provide a convenient handle for following the course of the rearrangement, as dichloroacetic acid, the unrearranged material, the ortho isomer and the para isomer all exhibited chemical shifts at 60 MC sufficiently different to allow their individual observation in the same reaction mixture. The acetyl methyl protons were similarly diagnostic, but the individual signals overlapped and were not completely resolved. The n.m.r. traces in Fig. 9 follow the course of the rearrangement catalyzed by dichloroacetic acid. Planimeter measurements on the relative areas of the $CHCl_2$- signal from the ortho and para isomers and the unrearranged material indicated that the ortho and para isomers are formed in yields of 75 per cent and 25 per cent respectively. Crude n.m.r. rate measurements on the rate of rearrangement at 40° in dichloroacetic acid solution, Fig. 9, show that the ortho and para isomers are formed with the same rate constant, and that the disappearance of the starting material occurs also with the same rate constant (k_{app} = 0.0052 min^{-1}., $t_{\frac{1}{2}}$ = 130 min.). Similar results were obtained from an n.m.r. study in methoxyacetic acid, where the rearrangement has a half life of ~80 hrs. at 30°. However, in this solvent, the chemical shifts of the dichloromethyl protons of the ortho and para isomers were not sufficiently different to allow their resolution, although the difference between the chemical shift of the dichloromethyl proton in the unrearranged material and the products was sufficient to allow the kinetics of disappearance and formation to be followed.

The fact that no dichloroacetic acid was formed during the course of the reaction rules out any mechanistic similarity of this rearrangement

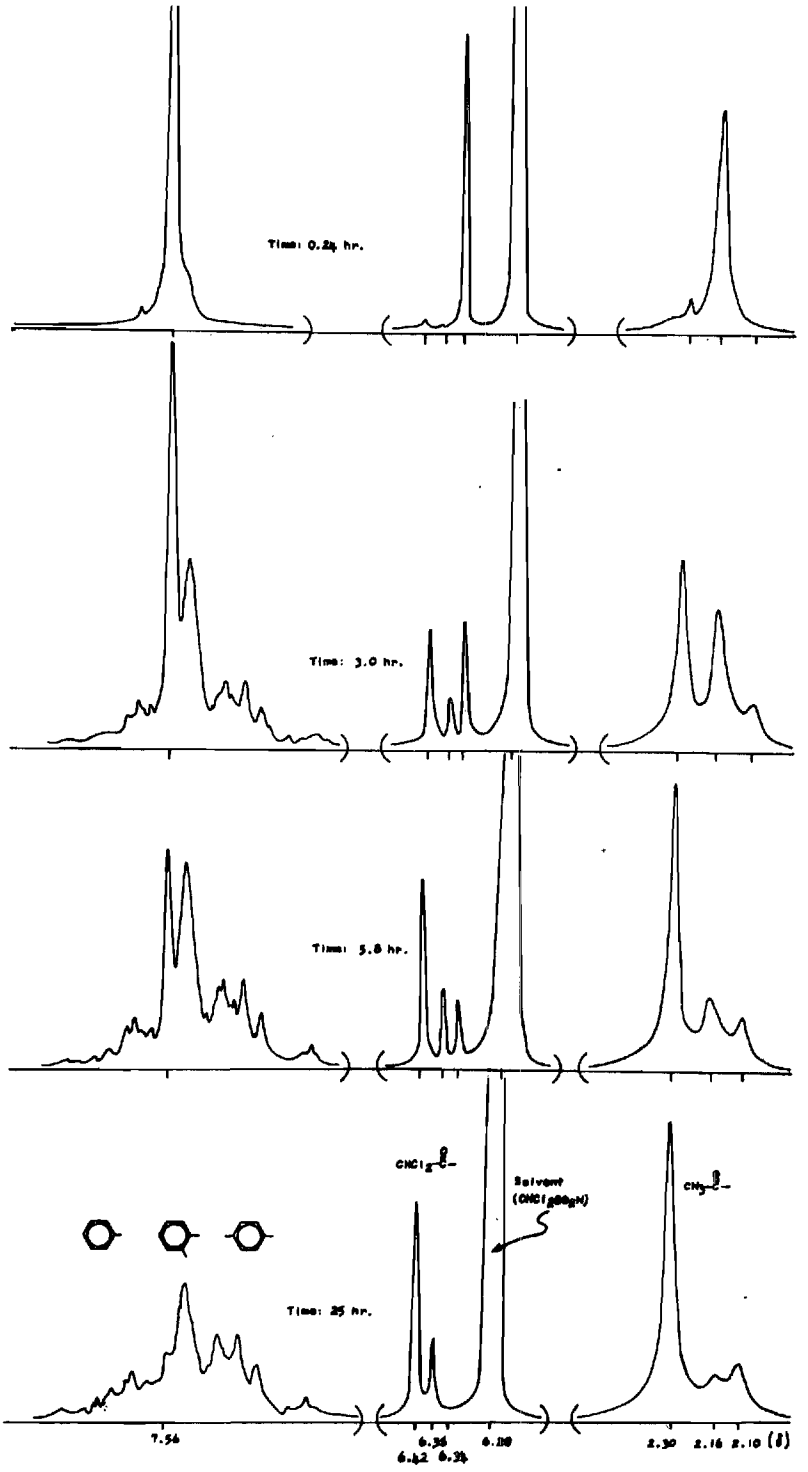


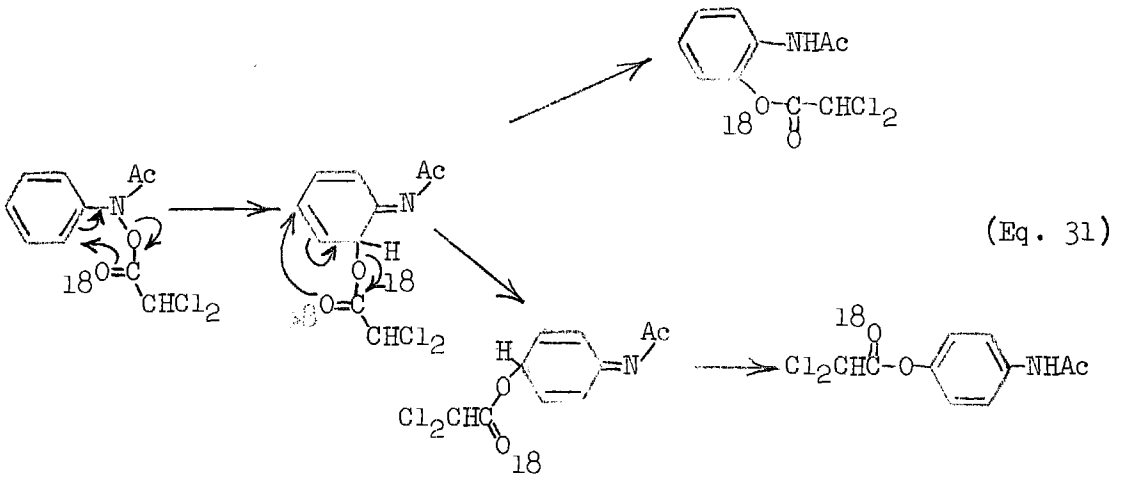
Figure 9. An N.M.R. Study of the Rearrangement of O-Dichloroacetyl-N-acetyl-N-phenylhydroxylamine in Dichloroacetic Acid Solvent.

to the acid-catalyzed intermolecular conversion of N-phenylhydroxylamine to o- and p- aminophenols,[52] since a similar pathway for this rearrangement would demand that the intermediate cationoid fragment react with the more nucleophilic methoxyacetic acid which is present in large excess, to form o- and p-esters of methoxyacetic acid, rather than combine with the dichloroacetic acid formed from heterolysis of the nitrogen-oxygen bond.

Attempted rearrangement of O-dichloroacetyl-N-acetyl-N-phenylhydroxylamine dissolved in carbon tetrachloride with concentrated sulfuric acid resulted in a violent reaction and decomposition to a blue, tarry material. The n.m.r. spectrum of this material indicated extensive decomposition had taken place.

The high yields of ortho products from the rearrangement of O-dichloroacetyl-N-acetyl-N-phenylhydroxylamine (as in the O-p-toluenesulfonyl-, O-methanesylfonyl-, and O-trifluoroacetyl- examples), the observation of identical rate constants for the formation of the ortho and para isomers and the lack of incorporation of methoxyacetic acid into the rearranging molecule strongly favor an intramolecular pathway.

The obvious dependence of the rate of these rearrangements on the electron-withdrawing inductive effect of the O-sulfonyl or O-acyl group (with qualitative rates of rearrangement in the order tosyl, mesyl> trifluoroacetyl > dichloroacetyl) and the deduced intramolecularity of these rearrangements suggest two possible pathways for these rearrangements. The first pathway (Eq. 31) envisages a concerted migration of the rearranging moiety to the ortho position in a fashion similar to the Claisen rearrangement.

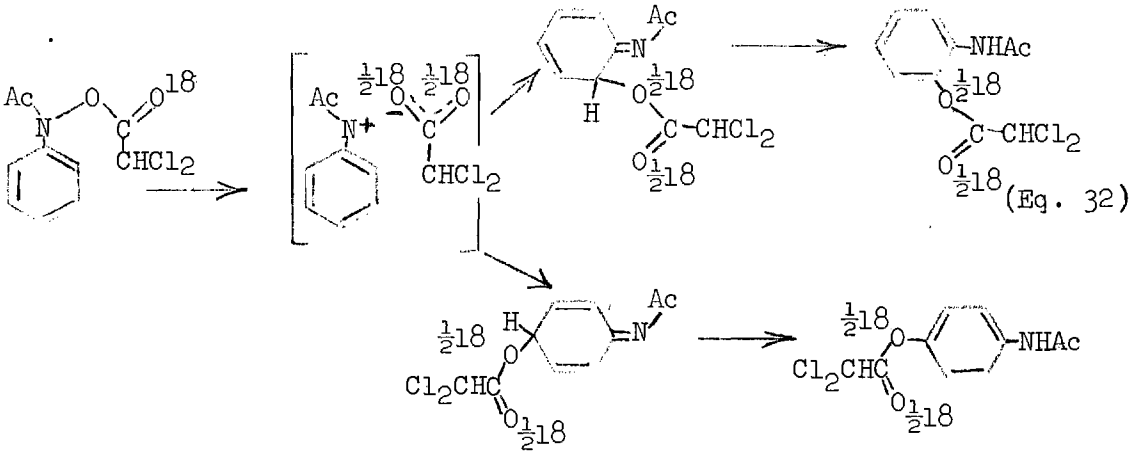


(Eq. 31)

The demonstrated sensitivity of this system to polar factors demands that the transition state for this step, which is a six-membered ring, be one in which the extent of nitrogen-oxygen bond heterolysis considerably exceeds the extent of carbon-oxygen bond formation. In contrast, the Claisen rearrangement has been found to be very insensitive to solvent polarity and to substituent effects.[91] The σ-complex resulting from this step can either undergo a second migration in Claisen fashion to the para position, or undergo a re-aromatization proton transfer to yield product.

The second pathway (Eq. 32) envisages a heterolytic cleavage of the nitrogen-oxygen bond, yielding a cationoid fragment and an anionoid fragment which are held together by electrostatic interactions. This intermediate then reacts in a second step to yield ortho or para σ-complexes which undergo re-aromatization proton transfers to yield products.

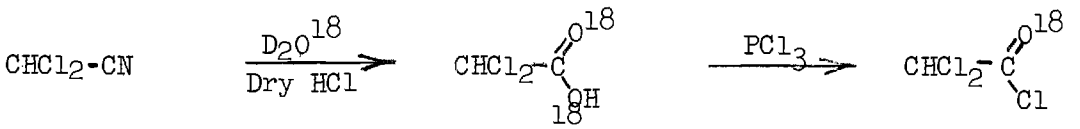
(91) See reference 27, pp. 507 ff.



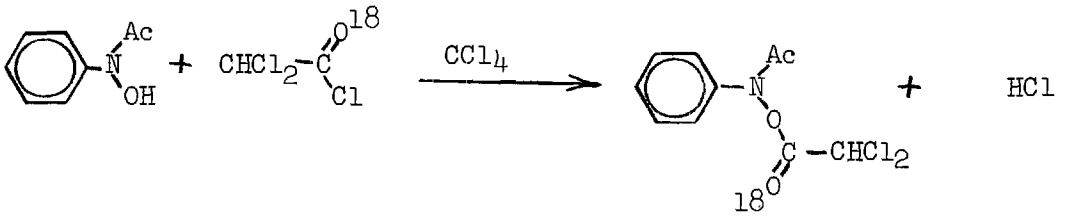
The first pathway clearly predicts that rearrangement of a derivative which contained isotopically labeled carbonyl or sulfuryl oxygens (as shown in Eq. 31) would result in an ortho isomer which had all of the label contained in its phenolic oxygen, while the para isomer would contain none of the label in its phenolic oxygen.

The second pathway, however, predicts that the carbonyl or sulfuryl oxygens lose their identity (as shown in Eq. 32) on formation of the anionoid fragment, and consequently, the phenolic oxygens in the rearrangement products would be expected to contain a statistical average of the enriched oxygen-18 isotope initially present in the carbonyl or sulfuryl oxygen atoms with the natural abundance of oxygen-18 present in the unlabeled oxygen atoms (assuming that the kinetic isotope effect on the collapse of the intermediate is negligible).

The rearrangement of O-dichloroacetyl-^{18}O-N-acetyl-N-phenylhydroxylamine (prepared by the synthesis shown in Eq. 33) provided a means for distinguishing between these two pathways. In addition, by carrying



(Eq. 33)



out the rearrangement in isotopically normal dichloroacetic acid, the intramolecularity of the rearrangement could be tested unambiguously. Table 7 compares the results of the mass spectral analysis of the o- and p-hydroxyacetanilides obtained from the hydrolysis of the products obtained from the rearrangement of O-dichloroacetyl-^{18}O-N-acetyl-N-phenylhydroxylamine in dichloroacetic acid with isotopically normal and authentic oxygen-18 labeled o-hydroxyacetanilide.

The data in Table 7 clearly demonstrate that on rearrangement, the labeled carbonyl oxygen atom and the hydroxylamine oxygen atom become nearly chemically equivalent, as the phenols from the labeling experiment are seen to contain only slightly more than half of the oxygen-18 enrichment present in the carbonyl group of the starting material (1.51 per cent oxygen-18 in the carbonyl oxygen and 0.20 per cent in the hydroxylamine oxygen). This fact clearly rules out the first pathway (Eq. 31) and lends strong support to the second pathway (Eq. 32), which allows the oxygens to become chemically equivalent during the course of the rearrangement. These data also unambiguously

Table 7. Mass Spectral Analysis

of the Products from the Rearrangement of

O-Dichloroacetyl-^{18}O-N-Acetyl-N-phenylhydroxylamine

Compound	Source	Intensity of isotope peaks of M, M 1 and M 2 and for the fragment resulting from loss of ketene. 151	152	153	^{18}O%*	109	110	111	^{18}O%
o-hydroxy-acetanilide	Authentic (isotopically normal)	100	11.9	1.27	-	-	-	-	-
"	^{18}O Labeling Experiment	100	11.1	2.24	0.96	-	-	-	-
p-hydroxy-acetanilide	Authentic (isotopically normal)	100	10.4	1.32	-	100	8.13	0.61	-
"	^{18}O Labeling Experiment	100	18.2	2.38	1.05	100	17.1	1.79	1.16

* Per cent oxygen-18 content in excess of the naturally occurring abundance.

show the rearrangement to be an intramolecular process, as exchange with the solvent would have resulted in phenols containing only a small fraction of oxygen-18 in excess of the natural abundance. It seems highly unlikely that the approximately 50 per cent decrease in oxygen-18 observed in both the ortho and para isomers is a result of contributions from an intermolecular component to the rearrangement.

O-Phenylhydroxylamines

The preparation of N-acetyl-O-phenylhydroxylamine as a stable, isolable compound, and the evidence for O-phenylhydroxylammonium

chloride suggest that the hypothetical O,N-diphenylhydroxylamine system should not be so unstable as to preclude the preparation and isolation of a suitably substituted O,N-diarylhydroxylamine, provided that a thermal rearrangement during synthesis can be avoided. The preparation of N-acetyl-O-phenylhydroxylamine and O-phenylhydroxylammonium chloride provides a new approach to synthesis in this area.

Acylation of 3,5-Dibromo-1-anilino-1-methylcyclohexadien-4-one with Acetic Anhydride

The isolation of 4-acetamido-2',6'-dibromo-4'-methyldiphenylether from the attempted acylation of the quinamine with acetic anhydride could have come about *via* rearrangement of the quinamine (catalyzed by a trace of acetic acid) followed by acylation of the product, or *via* the acylation of the quinamine followed by its rearrangement (thermal or acid catalyzed) to the observed product. More work is needed on this system in order to distinguish between these two possibilities. So far, attempts to acylate the quinamine under milder conditions have failed.

The Acid Catalyzed Reaction of N,S-Diphenylthiohydroxylamine

The failure of N,S-diphenylthiohydroxylamine to undergo an acid catalyzed rearrangement, yielding instead disproportionation products, is consistent with the usual reaction of sulfenic amides under acidic conditions.[92]

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(92) L. Zervas, D. Borovas and E. Gazis, *J. Am. Chem. Soc.*, 85, 3660 (1963).

CHAPTER VI

CONCLUSIONS

The Rearrangement of N-Acetylhydrazobenzene and the Rearrangement of O-Derivatives of N-Acetyl-N-phenylhydroxylamine

The spontaneous rearrangement of O,N-diphenyl-N-acetyl-hydroxylamine to 2'- and 4'-hydroxy-4-acetamidobiphenyls under the mild, non-acidic conditions of its synthesis cannot be simply rationalized as the result of an inherent instability of the O-arylhydroxylamine structure, since N-acetyl-O-phenylhydroxylamine and O-phenylhydroxylammonium chloride are both moderately stable, isolable materials. The striking similarity of the rearrangement products to those obtained from the rearrangement of hydrazobenzene, and the strong evidence presented in this thesis for an intramolecular pathway make it highly likely that this rearrangement is a good mechanistic analog of the benzidine rearrangement. The spontaneity of the rearrangement can then be rationalized as resulting from the electron-withdrawing inductive effect of the N-acetyl substituent coupled with the greater electronegativity of the O-phenyl oxygen as compared to nitrogen. These inductive electronic effects, which result in a net electron impoverishment of the nitrogen-oxygen bond, are envisaged to usurp the catalytic role of the protons in the acid-catalyzed benzidine rearrangement. That the N-acetyl group actually functions in this capacity is clearly indicated by the first-order dependence on the

Hammett acidity of rate of the demonstrated intramolecular rearrangement of N-acetylhydrazobenzene to N-acetylbenzidine in concentrated perchloric acid. Whether or not the net effect of the N-acetyl group and the oxygen substitution for nitrogen in the O,N-diphenyl-N-acetylhydroxylamine system are equivalent to one or two protons can be deduced only by investigating an O,N-diarylhydroxylamine which does not contain the N-acetyl substituent.

The novel rearrangement of O-p-toluenesulfonyl-O-methanesulfonyl-, O-trifluoroacetyl- and O-dichloroacetyl- derivatives of N-acetyl-N-phenylhydroxylamine to the corresponding o- and p- isomers, the lack of rearrangement of the O-p-nitrobenzoyl- and O-acetyl derivatives of N-acetyl-N-phenylhydroxylamine and the oxygen-18 labeling studies on the rearrangement of O-dichloroacetyl-^{18}O-N-acetyl-N-phenylhydroxylamine, which establish the intramolecularity of these rearrangements and eliminate a Claisen-like pathway for the rearrangement, clearly are in accord with the hypothesis that these rearrangements have mechanistic features in common not only with the rearrangement of O,N-diphenyl-N-acetylhydroxylamine, but also with the benzidine rearrangement. In particular, if it is accepted that these rearrangements are good mechanistic analogs of the benzidine rearrangement, they provide the first unambiguous evidence concerning the electronic nature of the bond cleavage in the benzidine rearrangement, as the trend of the relative rates of these rearrangements (tosyl, mesyl $>$ trifluoroacetyl $>$ dichloroacetyl) and the finding that the carbonyl oxygen and the hydroxylamine oxygen become nearly chemically equivalent during the course of the rearrangement clearly support a

heterolytic cleavage of the nitrogen-oxygen bond in these examples, and by analogy, a heterolytic cleavage of the nitrogen-nitrogen bond in the benzidine rearrangement--a conclusion which is in direct support of the Ingold bonding picture. Furthermore, the rearrangement of the incipient tosylate, mesylate, trifluroacetate, and dichloroacetate moieties clearly argues against the strong, dative, Π-bonding picture envisaged by Dewar.[30] However, the spontaneous rearrangement of O,N-diphenyl-N-acetylhydroxylamine, which generates an incipient phenoxide moiety on heterolysis of the nitrogen-oxygen bond, suggests that factors other than the leaving group stability can be of importance in lowering the activation energy for rearrangement, since phenoxide is several orders of magnitude less stable as a leaving group than acetate, which was found not to rearrange. Perhaps the reactivity of this system resides in contributions from charge-transfer complexing as well as electrostatic interactions which contribute to the stabilization of the transition-state for bond scission.

It is concluded that the new rearrangements and the mechanistic studies on these rearrangements presented in this thesis have general mechanistic features in common with the benzidine rearrangement, and as a result, they provide new information bearing on the mechanism of the benzidine rearrangement. In particular, the work in this thesis demonstrates that bond scission in these rearrangements is best described as a heterolytic process, and that bonding interactions between the fragments resulting from heterolysis are primarily electrostatic in nature, but depending on the exact system, may have important contributions

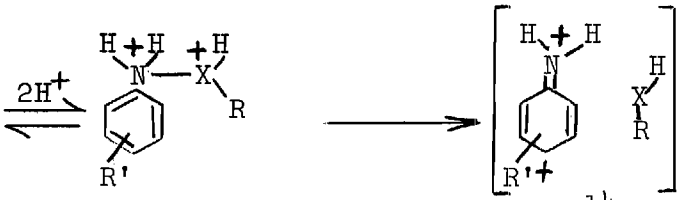
from charge-transfer complexing and ion-dipole interactions.

In addition to the mechanistic implications of these new rearrangements, they provide a synthetic method for preparing o-aminophenols and their derivatives that appears to be more convenient, at least on a laboratory scale, then existing procedures. The trifluoroacetyl system is particularly suited for synthetic usage as a result of its rapid rate of rearrangement and the ease with which the rearrangement product is hydrolyzed to the corresponding phenol.

A General Mechanism for the Benzidine and Related Rearrangements

While recognizing the difficulties attending broad generalizations concerning reaction mechanisms, the purpose of this section of the thesis is to propose that the Ingold mechanism for the benzidine rearrangement, with secondary modifications, can be generalized to satisfactorily describe, not only the new rearrangements reported herein, but also the quinamine rearrangement, the nitramine rearrangement and the rearrangement of sulfamic acid.

Eqs. 34, 35 and 36 together comprise a general statement of the electronic similarities and differences which exist among the spontaneous (thermal), one proton and two proton catalyzed rearrangements respectively.

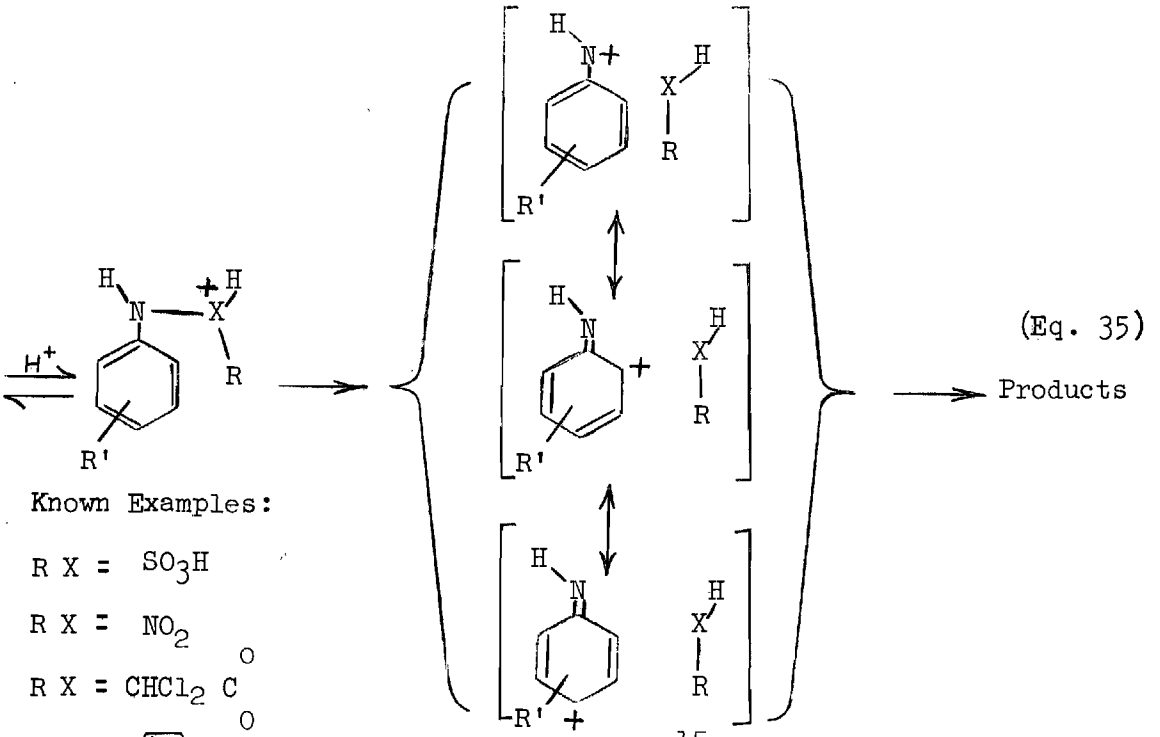


(Eq. 34)

14

Known Examples:

R X = Ar-NH- (Most Hydrazoaryls)



(Eq. 35)

Products

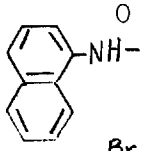
15

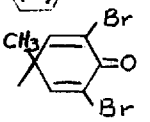
Known Examples:

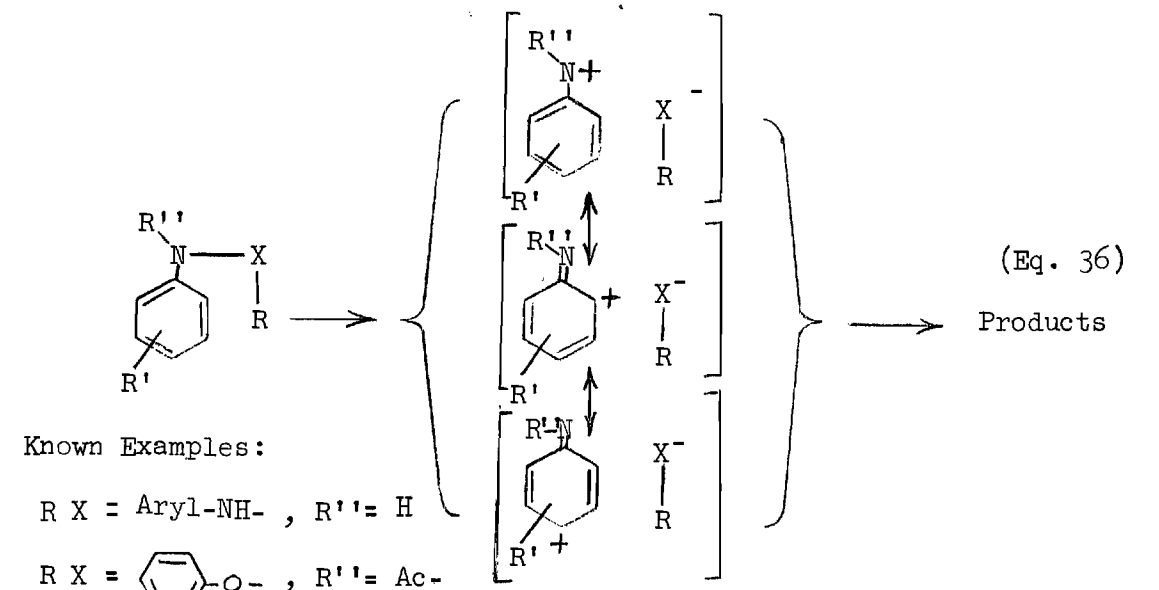
R X = SO_3H

R X = NO_2

R X = $CHCl_2C(=O)$

R X =  (and Certain Other Hydrazoaryls)

R X =  (and Other Quimamines)



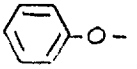
(Eq. 36)

Products

16

Known Examples:

R X = Aryl-NH- , R'' = H

R X =  , R'' = Ac-

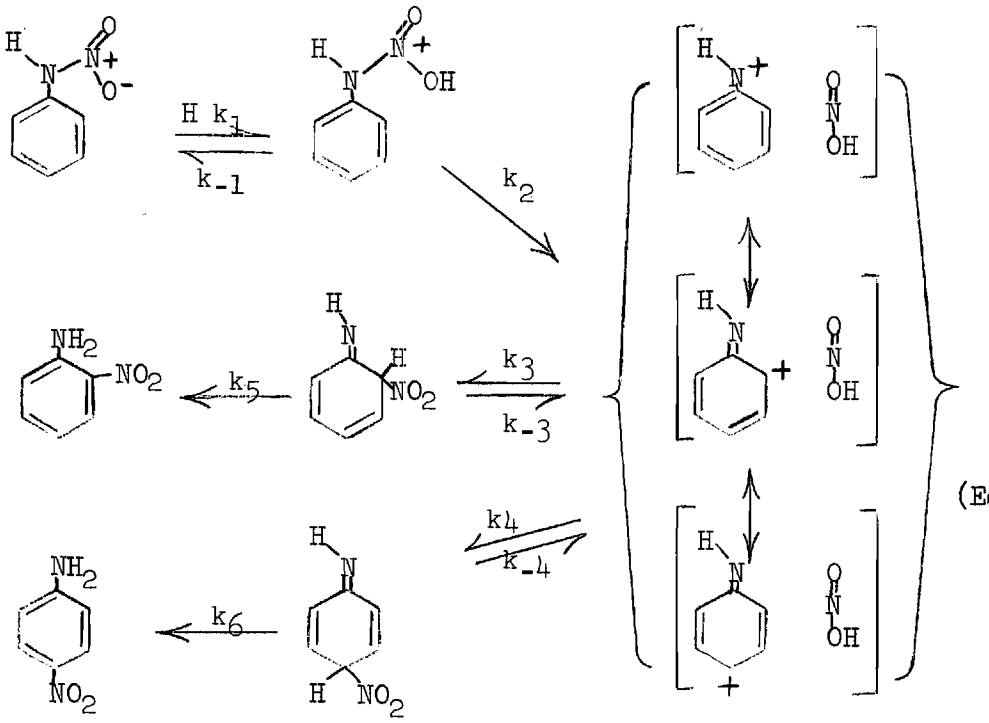
R X = H_3C-  , R'' = Ac-

R X = CF_3CO_2- , R'' = Ac-

It is not clear from the available experimental evidence whether or not structures 14, 15 and 16 represent transition states (energy maxima) or transient intermediates (shallow energy minima in the vicinity of the transition state) along the reaction coordinate, except in the case of the nitramine rearrangement[46,49] where there is a substantial amount of accumulated evidence which indicates that a definite intermediate is involved. Also, it has not been demonstrated explicitly that the rate limiting transition state involves bond scission, although all of the experimental evidence thus far gathered, with the possible exception of the small substrate deuterium kinetic isotope effect observed in the thermal rearrangement of 1,1'-hydrazonaphthylene, indicates that such is the case.

The details of the one and two proton mechanisms as they apply to the benzidine rearrangement have been adequately discussed in Chapter II and this discussion will not be repeated. The inclusion of the nitramine rearrangement within the general framework of the proposed mechanisms (Eq. 35) provides a third alternative to the mechanisms proposed for this rearrangement by White[48] and by Banthorpe and Hughes.[49] For this reason, the general mechanism, as applied to the nitramine rearrangement is here discussed in greater detail (Eq. 37), although no experimental work on the rearrangement of N-nitroanilines is presented in this thesis.

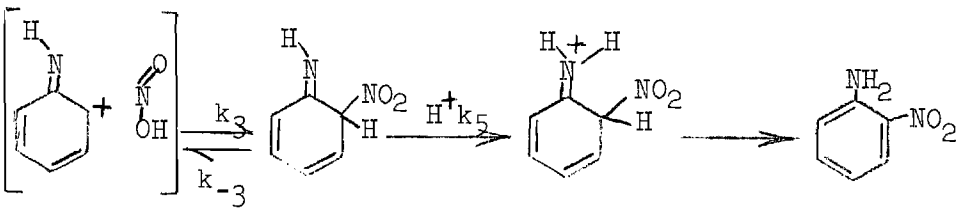
The merits of this new proposal are first, that it has considerable analogy with the rearrangement of O-dichloroacetyl-N-acetyl-N-phenylhydroxylamine (which is demonstrated by the work presented in this thesis



(Eq. 37)

to proceed via heterolytic bond cleavage to a positively charged fragment and an incipient dichloroacetic acid fragment) by invoking a protonation at the N-nitro oxygen rather than at the aryl nitrogen, followed by heterolysis of the nitrogen-nitrogen bond to form a similar positive fragment and an incipient nitrous acid fragment. Second, it conveniently explains the observation of nitrous acid among the reaction products by allowing a molecule of nitrous acid to escape from the resulting intermediate. Finally, it deals quite satisfactorily with the observed change in the o-/p- product ratio which occurs with a change in the acidity of the reaction medium by invoking a second kinetically unimportant protonation which takes place on the imine nitrogen (step k5) of the kinetically favored ortho σ-complex (as shown in Eq. 37), catalyzing a

re-aromatization proton loss from the ortho position. Neither the White nor the Banthorpe-Hughes mechanism can readily explain the dependence of the product ratio on acid concentration, because their mechanisms envisage the kinetically important protonation to take place on the amine nitrogen, making the second kinetically unimportant protonation impossible.



(Eq. 38)

Thus under conditions of high acidity, the ortho isomer is favored by kinetic processes, while under conditions of low acidity, where protonation of the weakly basic imine nitrogen is less favorable, a situation of thermodynamic product control is approached as a result of the reversibility of σ-complex formation.[93]

This mechanism is clearly capable of accommodating all of the known facts about the nitramine rearrangement, and it succeeds in circumventing the problem of an adequate mechanistic precedent which the Banthorpe-Hughes mechanism lacks. A similar mechanism can be envisaged for the sulfamic acid rearrangement, although this rearrangement is insufficiently characterized to allow a detailed discussion of mechanism.

(93) A reversible σ-complex formation is demanded also by the substrate deuterium isotope effect on the o-/p- product ratio observed by Banthorpe, et al.[49]

CHAPTER VII

RECOMMENDATIONS FOR FUTURE WORK

Synthesis of O,N-Diarylhydroxylamines

The results derived from the reaction of N-acetyl-N-phenylhydroxylamine with diphenyliodonium ion indicate that this synthetic approach should be pursued further. In particular, the reaction should be attempted with N-alkyl-N-phenylhydroxylamines which can be prepared by the reaction of N-phenylhydroxylamine with primary alkyl bromides in pyridine.[54] The reaction of N-phenylhydroxylamine with diphenyliodonium ion[71] is apparently complicated by disproportionation reactions and does not yield benzidine-like rearrangement products.

O-Phenylhydroxylamine and N-alkyl derivatives similarly provide an alternate approach to O,N-diarylhydroxylamine synthesis which looks promising. Here again, diphenyliodonium ion would appear to be a useful phenylating reagent.

Experiments with O-Aryl-N-acetyl-N-phenylhydroxylamines

The work presented in this thesis has established the broad outlines of the mechanistic features of this rearrangement. However, it remains to be shown whether or not the rearrangement involves a transient intermediate as has been deduced for the nitramine rearrangement.

An experiment which could provide evidence bearing on this question is the investigation of substrate deuterium isotope effects on both the rate of rearrangement and the *o*-/*p*- ratio. In this connection,

the finding of an effect on the product ratio by changes in the acidity of the reaction medium would add support for an intermediate.

Detailed kinetic studies on the rate of rearrangement of O-dichloroacetyl-N-acetyl-N-phenylhydroxylamine in media of varying acidity should be carried out to firmly establish the suspected acid catalysis of this rearrangement, and in the event that acid catalysis is found, to establish whether or not the rate of the rearrangement is a function of the Hammett acidity. Solvent deuterium isotope effects should be particularly diagnostic in differentiating between general or specific acid catalysis.

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In 1958, he married the former Linda L. Paige of Grand Junction, Colorado. The Dunn's presently have two children--Ken Michael, age six and Keith Allen, age four.